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Non-catalytic conversion of C–F bonds of *gem*-difluoromethylene derivatives to C–H bonds with lithium aluminum hydride under room temperature

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ABSTRACT

An unexpected hydrodefluorination of unactivated aliphatic C–F bonds of CF_2 derivatives with $LiAlH_4$ at room temperature without any added metal catalyst was reported. Deuterium-labeling experiments suggested that the hydrogens introduced into the products originated from $LiAlH_4$.

1. Introduction

With the development of fluorine chemistry and fluorine industry, more and more fluorinated compounds have been manufactured and found wide applications in refrigerants, pharmaceuticals, agrochemicals, and polymers.[1] But at the same time, hundreds of thousands of tons of fluorine-containing industrial pollutants, especially for these difluoromethylene-containing wastes, have been produced and contaminated our environment.[2] For example, difluorodichloromethane (Freon-12), one of the most important chlorofluorocarbons (CFCs), is responsible for the depletion of the ozone layer. Difluoromethane (HFC-32), a hydrofluorocarbon (HFC) compound used as an alternative to ODS (ozone depleting substance), is a relatively potent greenhouse gas.[3] How to treat these ubiquitous environmental contaminants is not only a great challenge for the chemist but also for the environmentalist.

The carbon–fluorine bond is the strongest single bond, which carbon can form.[4] The activation and functionalization of organofluorine compounds attract much interest from synthetic organic chemists. It represents an important functional group transformation and occupies a prominent position in modern fluorine and organometallic chemistry. Over the past decade, there has been considerable progress in the field of transition metal-promoted activation and cleavage of C–F bonds in fluoroarenes, fluoroalkenes, and α,α,α-trifluorotoluene derivatives.[5] In general, conversion of carbon–fluorine bond to carbon–hydrogen bond is the simplest but efficient method for decomposing and detoxifying of these various fluorinated compounds. Up to now, great efforts have been made to develop both new transition metal catalysts and novel reductants for the hydrodefluorination of fluorobenzene and fluorinated alkenes.[6] For example, Milstein et al. reported the hydrodefluorination of polyfluorobenzenes in the presence of hydrosilanes using of rhodium complexes as catalysts.[6h] More recently, Ozerov et al. used a class of carborane-supported silylium compounds as stable catalysts for hydrodefluorination of trifluoromethyl and nonafluorobutyl groups with silanes as the hydrogen source.[5g–i,6a] The trifluoromethyl group in conjugation with an acidic NH group was highly reactive and the trifluoromethylated compounds could be reduced with $LiAlH_4$ to give the corresponding methyl derivatives in low to moderate yields.[7] Fuchibe and Akiyama have taken a great interest in C–F bond activation and reduction. They found that the strong C–F bonds in fluorobenzenes and benzotrifluorides could be hydrodefluorinated with $LiAlH_4$ in refluxing dimethoxyethane or 1,4-dioxane using niobium (V) chloride as catalyst.[8] They also indicated that in the absence of $NbCl_5$, the reduction did not proceed to completion and gave the mixture of starting materials, complete and partially reduced products, whereas the yield of expected completely hydrodefluorinated product was very low.[8b]

Despite such encouraging developments of hydrodefluorination of C–F bond, examples of hydrodefluorination or activation of difluoromethylene derivatives remain very scarce. Generally speaking, the C–F bond in aliphatic fluoride becomes shorter and

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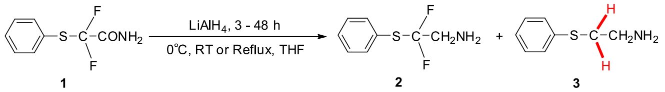
stronger as the number of fluorine atoms attached to the same carbon atom incereases.[9] Consequently, thermal stability and chemical resistance of C–F bond in difluoromethylene group is lower than that of C–F bond in trifluoromethyl group. This suggests that hydrodefluorination or functionalization of C–F bond in difluoromethylene group might be achieved under relatively mild reaction conditions.

Herein, we described an unexpected hydrodefluorination of unactivated aliphatic C–F bonds of CF_2 groups using widely accessible $LiAlH_4$ at room temperature without any additional metal catalyst.

2. Result and discussion

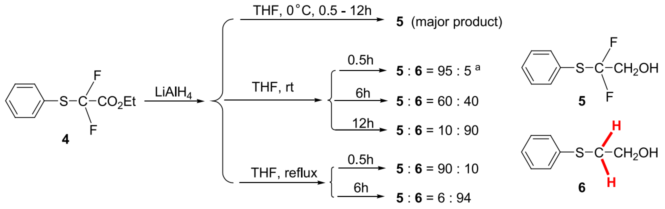
During the course of our recent investigation on the preparation of 2,2-difluoro-2-(phenylthio)ethylamine **2**,[10] when 2,2-difluoro-2-(phenylthio)acetamide **1** was reduced with $LiAlH_4$ in THF at reflux, in addition to normal reduction product **2**, an unexpected hydrodefluorination product **3** was also observed (Scheme 1). Furthermore, the ratio of **2** and **3** depended on the reaction conditions, such as temperature, time, and solvent.



Scheme 1. Reduction of 2,2-difluoro-2-(phenylthio)acetamide **1** with $LiAlH_4$.

The reduction of organic halides with $LiAlH_4$ is well documented.[11] However, the reduction of organic fluorides is not usually achieved with $LiAlH_4$ under mild conditions and in most cases stoichiometric or catalytic amount of the transition metal must be used or specific directing groups on the substrate are required.[12] Intrigued by the above preliminary experimental observations, we made every effort to elucidate details of this surprising reaction. Firstly, we used ethyl 2,2-difluoro-2-(phenylthio)acetate **4** as a model substrate. Compound **4** was allowed to react with $LiAlH_4$ (4 equiv) in THF under argon for 0.5–12 h at 0 °C, room temperature or reflux temperature, respectively. The results were summarized in Scheme 2. As can be seen from Scheme 2, the ratio of **5** and **6** was significantly affected by the reaction temperature and time. Generally, prolonged reaction times and high temperatures tended to produce hydrodefluorination product **6**. Much to our surprise, the reduction of CF_2 also proceeded smoothly to afford the corresponding methylene derivative in good yield at room temperature, but required longer time. Although the conversion of CF_2 to CH_2 with $LiAlH_4$ at refluxing temperature was proved to be successful in a relatively short period of time, energy-saving consideration prompted us to perform this hydrodefluorination at room temperature in the following study.

The other factor that has to be taken into consideration is that at room temperature $LiAlH_4$ is usually stable and has a better solubility in THF or diethyl ether.[13]



Scheme 2. Reduction of ethyl 2,2-difluoro-2-(phenylthio)acetate **4** with $LiAlH_4$ (4 equiv) under different reaction conditions. [a]The ratios of **5** and **6** were determined by GC analysis.

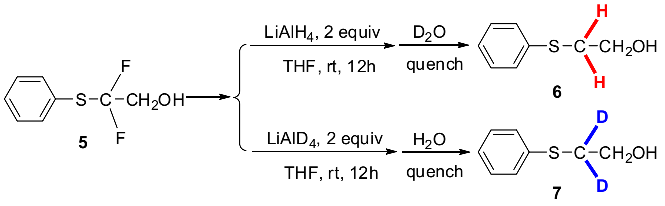
The influence of solvents on the yields of the reduction of **4** with $LiAlH_4$ at room temperature was also investigated (Table 1). Both THF and diethyl ether were found to be the most suitable solvents (Table 1, entries 1 and 3).

Table 1
Effects of the solvents on the reduction of **4**

Entry	Solvent[a]	**5**/%[b]	**6**/%[b]
1	THF	10	75
2	Toluene	53	13
3	Et_2O	12	73
4	1,4-Dioxane	70	10
5	Hexane	85	—

[a] Conditions: $LiAlH_4$ (4 equiv), 12 h, room temperature.
[b] Yields were based on GC analysis.

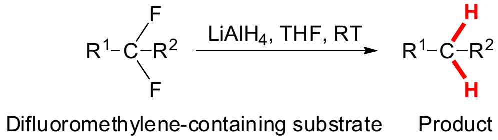
In order to probe the source of hydrogen for the reduction, the deuterium-labeling experiments were performed. When 2,2-difluoro-2-(phenylthio)ethanol **5** was reacted with $LiAlH_4$ in THF solution at room temperature for 12 h and then quenched with D_2O, no deuterium was incorporated into the product **6**. On the other hand, when the reduction of **5** was carried out with $LiAlD_4$ and quenched with H_2O, 2,2-dideuterio-2-(phenylthio)ethanol **7** was obtained (Scheme 3). The deuterium-labeling experiments proved that the hydrogens introduced into the products originated from $LiAlH_4$.



Scheme 3. The deuterium-labeling experiments on 2,2-difluoro-2-(phenylthio)ethanol **5**.

To determine the limitations of the method, we applied this reaction to several additional difluoromethylene-containing substrates (Table 2). Among the difluoromethylene substrates tested, most of them could be reduced in THF with $LiAlH_4$ at room temperature to give the corresponding products in moderate to good yields. Compound 2,2-difluoro-2-(phenylthio)ethanol **5**, which

Table 2
Hydrodefluorination of difluoromethylene-containing derivatives[a]



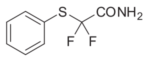
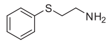
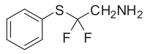
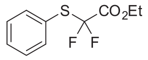
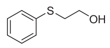
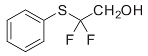
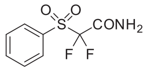
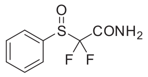
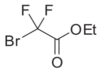
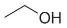
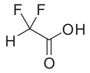
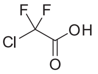
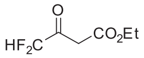
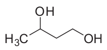
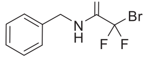
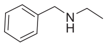
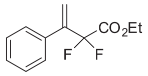
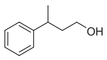
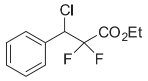
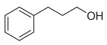
Entry	Substrate	$LiAlH_4$ (equiv)	Time/h	Product	Yield[b] (%)
1	 (**1**)	4	45	 (**3**)	78
2	 (**2**)	2	48	(**3**)	75
3	 (**4**)	4	12	 (**6**)	75
4	 (**5**)	2	10	(**6**)	80

Table 2 (*continued*)

Entry	Substrate	$LiAlH_4$ (equiv)	Time/h	Product	Yield[b] (%)
5	 **(8)**	6	52	(**3**)	48
6	 **(9)**	5	50	(**3**)	50
7	 **(10)**	5	18	 **(17)**	76
8	 **(11)**	4	18	(**17**)	78
9	 **(12)**	6	48	(**17**)	57
10[c]	 **(13)**	6	72	 **(18)**	61
11	 **(14)**	6	48	 **(19)**	62
12	 **(15)**	5	24	 **(20)**	64
13[c]	 **(16)**	5	36	 **(21)**	62

[a] Difluoromethylene compounds, $LiAlH_4$ (2–6 equiv), THF, room temperature.
[b] Yields were based on GC analysis.
[c] The reaction was carried out at 60 °C.

only has difluoromethylene group involved in the reduction reaction could afford the expected product in a relatively high yield (80%). The other difluoromethylene compounds bearing several functional groups, such as carbonyl, sulphonyl, halide (Cl and Br), double-bond, etc., could also be reduced stepwisely, but prolonged reaction time and more $LiAlH_4$ were required. It is obvious that the existence of multi-functional groups could significantly influence the yield for the whole reduction process. It should also be mentioned that no matter what the atom adjacent to the difluoromethyl group is, such as bromine, carbon, hydrogen, and sulfur, the hydrodefluorination proceeded smoothly.

It is well known that $LiAlH_4$ is capable of reducing only polarized π bonds, but is without action on the unpolarized π bond. Carbon–carbon double bonds can only be reduced with $LiAlH_4$ in the presence of first-row transition-metal halides or if they are made positive or activated to a great extent either through adjacent electrophilic groups.[14] In the case of ethyl 2,2-difluoro-3-phenylbut-3-enoate **15** (entry 12), it is noteworthy that both C–F bonds and C=C bond were reduced to give the corresponding primary alcohol **20** in 64% yield. The mechanism of double bond saturation is still uncertain, but it is apparent that the double bond in **15** is activated by the adjacent *gem*-difluoromethylene group.

3. Conclusion

In summary, we firstly reported the room temperature hydrodefluorination of nonactivated aliphatic C–F bonds of the CF_2 groups with $LiAlH_4$ in the absence of metal catalyst. It might be a simple, efficient, and practical method for the conversion of environmentally important fluorocarbons to the corresponding hydrocarbons.

4. Experimental

4.1. General

All reagents were of analytic grade and obtained from commercial suppliers and used without further purification. Anhydrous THF was distilled from sodium–benzophenone. $LiAlH_4$ was purchased from Shanghai Darui Finechemical Co., Ltd. and Shanghai Jiachen Chemical Industry Co. of China. $LiAlD_4$ was purchased from J & K Chemical Limited. All reactions were carried out under argon atmosphere with dry solvents. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer (400 MHz and 100 MHz, respectively) using TMS as internal standard and $CDCl_3$ as solvent. The ^{19}F NMR spectrum was obtained using a Bruker AM-400 spectrometer (376 MHz) and using CF_3CO_2H as external standard and $CDCl_3$ as solvent. Gas chromatography (GC) was recorded on HP 6890 Plus GC instrument and Gas chromatography-mass spectra (GC–MS) were recorded on HP 5973 MSD with 6890 GC. Both conventional and high resolution mass spectra were performed on a MicroMass GCT CA 055 instrument. Column chromatography was carried out with Merck 60 (230–400 mesh) silica gel.

4.2. Preparation of starting materials

The preparation of the substrates **1** and **3**–**5** has been reported previously.[10] Substrates **8**–**9** and **14**–**16** were prepared according to the literatures.[15–19] Substrates **10**–**13** were obtained from commercial suppliers.

*4.2.1. Ethyl 2,2-difluoro-3-phenylbut-3-enoate (**15**).* Light-yellow liquid, yield: 87%. ^1H NMR: δ 1.20 (t, J=7.1 Hz, 3H), 4.25 (q, J=7.1 Hz, 2H), 5.75 (s, 1H), 5.93 (s, 1H), 7.37–7.43 (m, 5H). ^{13}C NMR: δ 13.7, 63.0, 113.1 (t, $^1J_{CF}$=252.0 Hz), 120.1 (t, $^3J_{CF}$=8.5 Hz), 127.8, 128.1, 128.4, 128.7, 141.4 (t, $^2J_{CF}$=22.1 Hz), 163.6 (t, $^{2'}J_{CF}$=34.0 Hz). ^{19}F NMR: δ −79.1 (s, 2F). GC–MS: m/z=226 (87), 198 (23), 153 (100), 133 (57), 103 (41), 77 (15).

4.3. Hydrofluorination of *gem*-difluoromethylene derivatives

*4.3.1. 2-(Phenylthio) ethanol (**6**).*[20] To a suspension of lithium aluminum hydride (151 mg, 4 mmol) in anhydrous THF was added dropwise to a THF solution of ethyl 2,2-difluoro-2-(phenylthio)acetate **4** (232 mg, 1 mmol) at 0 °C under argon atmosphere. The mixture was then warmed to room temperature and stirred for 12 h (TLC). The reaction was quenched with H_2O at 0 °C and stirred for 30 min. After filtering, the filtrate was extracted with ethyl acetate (20 mL×3) and washed with brine. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by chromatography to give the desired product **6** (158 mg) in 70% yield as a light-yellow liquid. ^1H NMR: δ 2.34 (s, 1H), 3.13 (t, J=6.0 Hz, 2H), 3.76 (t, J=6.0 Hz, 2H), 7.24–7.42 (m, 5H). ^{13}C NMR: δ 37.2, 60.4, 126.7, 129.1, 130.2, 134.9. MS (EI) m/z (relative intensity, %) 154 (M^+, 88), 123 (100), 110 (6).

*4.3.2. 2-(Phenylthio)ethylamine (**3**).*[21] Light-yellow liquid. ^1H NMR: δ 3.00 (t, J=6.2 Hz, 2H), 3.13 (t, J=6.3 Hz, 2H), 4.96 (s, 2H), 7.18–7.41

(m, 5H). ^{13}C NMR: δ 30.0, 62.5, 126.4, 129.0, 129.9, 135.4. MS (EI) m/z (relative intensity, %) 153 (M$^+$, 21), 124 (100), 109 (7).

*4.3.3. N-Benzylethylamine (**19**).*[22] Light-yellow liquid. ^{1}H NMR: δ 1.17 (t, J=7.1 Hz, 3H), 1.90 (s, 1H), 2.72 (t, J=7.2 Hz, 2H), 3.83 (s, 2H), 7.25–7.36 (m, 5H). ^{13}C NMR: δ 15.2, 43.6, 53.9, 126.9, 128.2, 128.4, 140.2. MS (EI) m/z (relative intensity, %) 135 (M$^+$, 16), 120 (37), 91 (100).

*4.3.4. 3-Phenylbutan-1-ol (**20**).*[23] Light-yellow liquid. ^{1}H NMR: δ 1.31 (d, J=7.0 Hz, 3H), 1.50 (s, 1H), 1.88 (m, J=7.0 Hz, 2H), 2.87–2.96 (m, 1H), 3.53–3.63 (m, 2H), 7.21–7.35 (m, 5H). ^{13}C NMR: δ 22.4, 36.5, 41.0, 61.2, 126.1, 127.0, 128.5, 146.9. MS (EI) m/z (relative intensity, %) 150 (M$^+$, 13), 132 (25), 117 (63), 105 (100), 91 (29), 77 (11).

*4.3.5. 3-Phenylpropan-1-ol (**21**).*[24] Light-yellow liquid. ^{1}H NMR: δ 1.28 (s, 1H), 1.89–1.96 (m, 2H), 2.74 (t, J=7.7 Hz, 2H), 3.71 (t, J=6.4 Hz, 2H), 7.20–7.43 (m, 5H). ^{13}C NMR: δ 32.1, 34.2, 62.3, 125.9, 128.4, 128.4, 141.8. MS (EI) m/z (relative intensity, %) 136 (M$^+$, 25), 117 (100), 91 (65), 77 (11).

4.4. Deuterium-labeling experiments

*4.4.1. 2,2-Deuterio-2-(phenylthio)-ethanol (**7**).* Compound **7** was prepared by the same procedure as used for **6** with the reductant lithium aluminum deuteride (LiAlD$_4$). Light-yellow liquid. ^{1}H NMR: δ 2.00 (s, 1H), 3.14 (t, J=5.9 Hz, 0.2H), 3.76 (s, 2H), 7.23–7.43 (m, 5H). ^{13}C NMR: δ 29.7 (t, J=33.9 Hz), 60.2, 126.7, 129.1, 130.3, 134.8. GC–MS: m/z=156 (91), 125 (100), 110 (48), 77 (11). HRMS calcd for $C_8H_8D_2OS$: 156.0578, found 156.0570.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.11.052.

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