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Short communication

α,α-Difluoro-α-phenylsulfanyl-α-trimethylsilylmethane as a difluoromethyl building block: A general strategy to α,α-difluoromethyl aryl ketones

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ABSTRACT

The synthetic utility of α,α-difluoro-α-phenylsulfanyl-α-trimethylsilylmethane ($PhSCF_2SiMe_3$; **1**) as a difluoromethyl building block providing a general strategy to α,α-difluoromethyl aryl ketones was demonstrated. Oxidation, by using *m*-chloroperoxybenzoic acid, of the readily available 1-aryl-2,2-difluoro-2-phenylsulfanyl-1-trimethylsiloxyethanes obtained from fluoride-catalyzed nucleophilic addition of $PhSCF_2SiMe_3$ with aromatic aldehydes followed by flash vacuum pyrolytic elimination provided α,α-difluoromethyl aryl ketones in moderate overall yields.

1. Introduction

α,α-Difluoromethyl ketones are important fluorine-containing building blocks in organic and medicinal chemistry [1]. Numerous synthetic methods for the preparation of these compounds, based on direct fluorination of nonfluorinated starting materials using various electrophilic fluorinating reagents, such as cesium fluoroxysulfate [2], 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor; F-TEDA-BF_4) [3], *N*-fluoro-bis[(trifluoromethyl)sulfonyl]imide [4], have been reported. However, these methods cannot be used as general strategies to *gem*-difluoromethylenated carbonyl compounds. On the other hand, the preparation of α,α-difluoromethyl ketones *via* the corresponding 2,2-difluoro enol derivatives, such as 2,2-difluoro enol esters [5] and 2,2-difluoro enol silyl ethers [6] has received more attention [7], because such compounds can be readily prepared from, for examples, trifluoroethanol [8], halodifluoromethyl ketones [9], trifluoromethylacylsilane [10], trifluoromethyl ketones [11], and trifluoromethyltrimethylsilane or perfluoroalkyl organometallics [12].

We have recently reported that $PhSCF_2SiMe_3$ (**1**) underwent fluoride-catalyzed nucleophilic addition to various aromatic aldehydes to provide the mixtures of 1-aryl-2,2-difluoro-1-hydroxy-2-phenylsulfanylethanes (**2**) and their silyl ether derivatives **3** which were easily separated by chromatography on silica gel [13]. Compounds of type **2** (R^1 = H, alkyl, aryl; R^2 = alkyl, aryl) have been demonstrated as useful precursors for the preparation of 1,1-difluoroalkenes (Scheme 1) [14].

Due to the readily available of the silyl ether derivatives **4**, obtained from the reaction of **1** with aromatic aldehydes, we envisioned that they could be employed as the starting materials for the preparation of α,α-difluoromethyl ketones **6** by pyrolysis of their sulfoxides **5** as summarized in Scheme 2.

2. Results and discussion

The oxidation of compound **4a** was first attempted using $NaIO_4$ in aqueous methanol at 0 °C to room temperature. The reaction proceeded incompletely, leading to a mixture of **3** (R^1 = H; R^2 = 4-MeOPh), **4a** and **5a** as well as the corresponding sulfones. However, the reaction employing *m*-CPBA (1.2 equiv.) in THF at −78 °C to room temperature overnight provided the expected sulfoxide **5a** in quantitative yield. Since the sulfoxide **5a** underwent O–$SiMe_3$ bond cleavage rapidly, it was directly subjected to flash-vacuum pyrolysis (FVP) to afford the expected 2,2-difluoro-1-(4-methoxyphenyl)ethanone (**6a**) in 44% yield (Entry 1, Table 1). 1-Aryl-2,2-difluoroketones **6b**–**6e** were also be prepared in moderate yields by using this approach (Entries 2–5, Table 1). The formation of aryl α,α-difluoromethyl ketones **6** resulted from the sulfoxide elimination of the sulfoxides **5** to afford the corresponding *gem*-difluoro silyl enol ethers, followed by hydrolysis (Scheme 2).

In conclusion, we have demonstrated the synthetic utility of $PhSCF_2SiMe_3$ (**1**) as difluoromethyl building block providing a general strategy to α,α-difluoromethyl aryl ketones.

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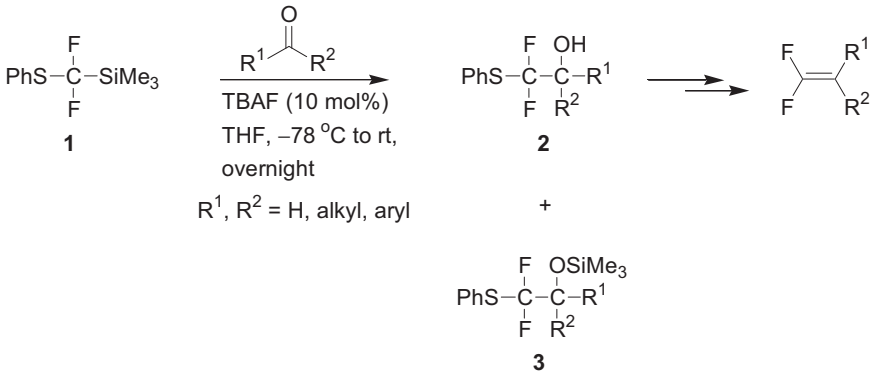


Scheme 1.

3. Experimental

The ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker DPX-300 or a Bruker DPX-400 spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. The ^{19}F NMR spectra were recorded on a Bruker DPX-400 (376 MHz) spectrometer and chemical shifts (δ) were measured with fluorotrichloromethane ($\delta = 0$) as an internal standard. The IR spectra were recorded on either a Jasco A-302 or a Perkin Elmer 683 infrared spectrometer. The electron impact mass spectra were recorded by using Thermo Finnigan Polaris Q mass spectrometer. The high resolution mass spectra were recorded on HR-TOF-MS Micromass model VQ-TOF2. Melting points were recorded on a Buchi 501 melting point apparatus and are uncorrected.

Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl. Other common solvents (hexane and ethyl acetate) were distilled before use. Column chromatography was performed using Merck silica gel 60H (Art. 7736). $PhSCF_2SiMe_3$ was prepared according to the literature procedure [15]. Compound **4** was prepared from $PhSCF_2SiMe_3$ and aromatic aldehydes according to the previous report [14].

3.1. Typical procedure for the preparation of compounds 6

A solution of compound **4a** (107 mg, 0.29 mmol) in dry THF (5 mL) at −78 °C was treated with a solution of 70% *m*-chloroperbenzoic acid (*m*-CPBA; 86 mg, 0.35 mmol) in dry THF (5 mL). The reaction mixture was stirred at −78 °C and slowly warmed up to room temperature overnight (12 h). The reaction mixture was quenched with a saturated $NaHCO_3$ solution (5 mL). The aqueous layer was extracted with EtOAc (3× 20 mL) and the combined organic phase was dried over anhydrous Na_2SO_4. After removal of the solvents under reduced pressure, the crude sulfoxide **5a** (117 mg) was directly subjected to flash-vacuum pyrolysis to give a crude mixture which was purified by chromatography to give the corresponding product **6a**.

3.1.1. 2,2-Difluoro-1-(4-methoxyphenyl)ethanone (6a) [3c,5]

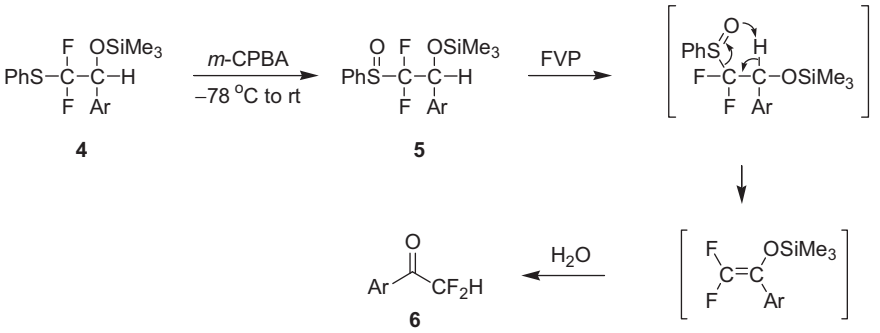
Pale yellow oil (24 mg, 44% yield); IR ($CHCl_3$): 1690 (s), 1602 (s), 1574 (s), 1514 (s), 1303 (s), 1266 (s), 1178 (s), 1139 (s), 1062 (s), 1029 (s) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, J = 9.1 Hz, 2H, ArH), 7.02–6.97 (m, 2H, ArH), 6.26 (t, J = 53.7 Hz, 1H, CHF_2), 3.91 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.7 (t, J = 24.9 Hz, CO), 165.6 (C), 132.8 (2× CH), 125.1 (C), 114.9 (2× CH), 112.1 (t, J = 252.4 Hz, CF_2), 56.3 (OCH_3). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −121.9 (d, J = 53.2 Hz, 2F, CF_2). MS (EI, m/z, %): 186 $[M]^+$ (1), 135 (100), 107 (10), 77 (39).

3.1.2. 2,2-Difluoro-1-(2,4-dimethoxyphenyl)ethanone (6b)

According to the general procedure, compound **4b** (104 mg, 0.26 mmol) was treated with 70% *m*-CPBA (77 mg, 0.31 mmol), followed by FVP to give compound **6b** (29 mg, 52% yield) as a white solid; mp: 72–73 °C. IR (KBr): 1666 (s), 1603 (s), 1257 (s), 1107 (s), 1017 (s) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, J = 8.8 Hz, 1H, ArH), 6.60 (dd, J = 2.3, 8.8 Hz, 1H, ArH), 6.58 (t, J = 53.9 Hz, 1H, CHF_2), 6.47 (d, J = 2.3 Hz, 1H, ArH), 3.93 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.3 (t, J = 23.9 Hz, CO), 167.0 (C), 162.3 (C), 134.5 (CH), 117.1 (C), 110.3 (t, J = 245.5 Hz, CF_2), 107.1 (CH), 99.0 (CH), 56.5 (OCH_3), 56.4 (OCH_3). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −128.6 (d, J = 53.8 Hz, 2F, CF_2). MS (EI, m/z, %): 216 $[M]^+$ (7), 165 (100), 122 (11), 77 (10). HRMS (EI): calcd. for $C_{10}H_{10}F_2O_3$: 216.0598; found: 216.0600.

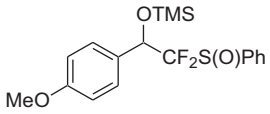
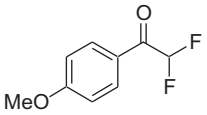
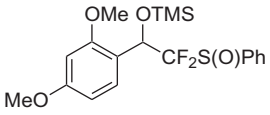
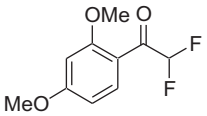
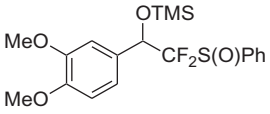
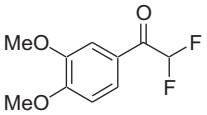
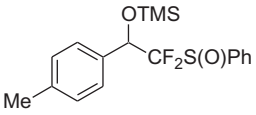
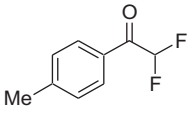
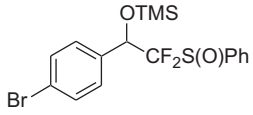
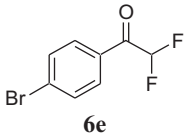
3.1.3. 2,2-Difluoro-1-(3,4-dimethoxyphenyl)ethanone (6c)

According to the general procedure, compound **4c** (110 mg, 0.28 mmol) was treated with 70% *m*-CPBA (81 mg, 0.33 mmol), followed by FVP to give compound **6c** (22 mg, 36% yield) as a pale yellow oil; IR ($CHCl_3$): 1691 (s), 1597 (s), 1518 (s), 1277 (s) cm^{-1}.



Scheme 2.

Table 1
Preparation of 1-aryl-2,2-difluoroketones **6** from compounds **4**.

Entry	4	5	FVP conditions (°C, mmHg)	6	Yield (%)[a]
1	**4a**	 **5a**	600, 0.03	 **6a**	44
2	**4b**	 **5b**	600, 0.03	 **6b**	52
3	**4c**	 **5c**	600, 0.05	 **6c**	36
4	**4d**	 **5d**	600, 0.05	 **6d**	37
5	**4e**	 **5e**	600, 0.03	 **6e**	46

[a] Isolated yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78–7.73 (m, 1H, ArH), 7.58 (d, J = 2.0 Hz, 1H, ArH), 6.95 (d, J = 8.4 Hz, 1H, ArH), 6.27 (t, J = 54.0 Hz, 1H, CHF_2), 3.99 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.9 (t, J = 23.9 Hz, CO), 155.6 (C), 150.1 (C), 125.7 (CH), 125.2 (C), 112.1 (t, J = 252.4 Hz, CF_2), 111.8 (CH), 111.0 (CH), 52.8 (OCH_3), 56.7 (OCH_3). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −121.3 (d, J = 53.8 Hz, 2F, CF_2). MS (EI, m/z, %): 216 $[M]^+$ (30), 165 (100), 122 (14), 107 (11), 77 (44). HRMS (EI) calcd. for $C_{10}H_{10}F_2O_3$: 216.0598; found: 216.0605.

3.1.4. 2,2-Difluoro-1-(4-methylphenyl)ethanone (6d) [6]

According to the general procedure, compound **4d** (105 mg, 0.30 mmol) was treated with 70% m-CPBA (89 mg, 0.36 mmol) followed by FVP to give compound **6d** (19 mg, 37% yield) as a colorless oil; IR (neat): 1705 (s), 1608 (s), 1299 (m), 1138 (m), 1064 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (d, J = 8.1 Hz, 2H, ArH), 7.32 (d, J = 8.1 Hz, 2H, ArH), 6.27 (t, J = 53.6 Hz, 1H, CHF_2), 2.45 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.2 (t, J = 25.0 Hz, CO), 146.2 (C), 129.7 (t, J = 2.3 Hz, 2× CH), 129.7 (2× CH), 129.0 (t, J = 1.8 Hz, C), 111.3 (t, J = 252.3 Hz, CF_2), 21.9 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −122.3 (d, J = 54.1 Hz, 2F, CF_2). MS (EI, m/z, %): 171 $[M+H]^+$ (1), 165 (7), 154 (17), 119 (100), 109 (8), 91 (49), 65 (26).

3.1.5. 1-(4-Bromophenyl)-2,2-difluoroethanone (6e) [1f,3d,6]

According to the general procedure, compound **4e** (100 mg, 0.24 mmol) was treated with 70% m-CPBA (71 mg, 0.29 mmol), followed by FVP to give compound **6e** (26 mg, 46% yield) as a colorless oil; IR (neat): 1715 (s), 1587 (s), 1073 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (d, J = 8.3 Hz, 2H, ArH), 7.60 (d, J = 8.6, 2H, ArH), 6.29 (t, J = 53.4 Hz, 1H, CHF_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.7 (t, J = 26.0 Hz, CO), 132.3 (2× CH), 130.9 (t, J = 2.5 Hz, 2× CH), 130.5 (C), 130.1 (t, J = 2.1 Hz, C), 111.3 (t, J = 252.7 Hz, CF_2). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −122.0 (d, J = 53.0 Hz, 2F, CF_2). MS (EI, m/z, %): 235 (11), 197 (14), 149 (47), 97 (52), 85 (68), 77 (34).

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[13] Compounds **3** and **4** are relatively stable, and could be purified by chromatography on silica gel.

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