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Journal of Fluorine Chemistry 129 (2008) 382–385
JOURNAL OF FLUORINE CHEMISTRY
www.elsevier.com/locate/fluor

Fluoride ion-mediated nucleophilic fluoroalkylation of alkyl halides with Me_3SiCF_2SPh: Synthesis of $PhSCF_2$- and CF_2H-containing compounds

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Received 10 January 2008; received in revised form 21 January 2008; accepted 22 January 2008
Available online 2 February 2008

Abstract

A facile and highly efficient nucleophilic (phenylthio)difluoromethylation of alkyl halides has been achieved via fluoride ion-mediated substitution reaction using [difluoro(phenylthio)methyl]trimethylsilane (Me_3SiCF_2SPh). The reaction proceeds well with primary alkyl bromides (or alkyl iodides) in DME solvent when CsF/15-crown-5 was used as the fluoride source/additive. The $PhSCF_2$-containing products can be readily transformed into CF_2H-containing compounds via a free-radical desulfurization method.

Keywords: (Phenylthio)difluoromethylation; Difluoromethylation; Selective fluoroalkylation; Nucleophilic substitution; Alkyl halides

1. Introduction

Selective incorporation of fluorine atom(s) or a fluorinated moiety into an organic molecule can often bring profound effects on its chemical and biological properties, including changes in stability, lipophilicity, and bioavailability [1–7]. As a result, organofluorine chemistry has attracted enormous attention in the field of pharmaceutical and agricultural chemistry, as exemplified by the fact that fluorine substituents have become widespread and important drug components [8,9]. Among fluorine-containing moities, the difluoromethyl group (CF_2H) is of significant interest [10–13], since the latter one is believed to act as an isopolar and isosteric analog of the CH_2OH group [14,15]. Moreover, CF_2H is able to act as a lipophilic hydrogen bond donor through hydrogen bonding [11].

There are several methods for introducing the CF_2H moiety [4,5,7,16], including (a) the deoxofluorination of aldehydes using SF_4, DAST, or SeF_4 reagent [17,18], (b) nucleophilic fluorination of gem-bistriflates using TBAF [19], (c) fluorination of 1,2- or 1,3-dithianes using BrF_3 [12,20,21], (d) the addition of CBr_2F_2 to double bonds [22], (e) $S_{RN}1$ reaction between a nucleophile and $CHClF_2$ [5,23], and (f) nucleophilic introduction of a CF_2H moiety into carbonyl compounds using (difluoromethyl)dimethylphenylsilane [24] or difluoro[bis(trimethylsilyl)]methane [10]. More recently, both difluoromethyl phenyl sulfone ($PhSO_2CF_2H$) and [difluoro(phenylsulfonyl)methyl]trimethylsilane ($Me_3SiCF_2SO_2Ph$) were used as efficient nucleophilic difluoromethylating agents for a variety of electrophiles [25].

Recently, Tyrra et al. reported a fluoride ion-mediated cross-coupling of alkyl halides RX (X = Br, I) and Me_3SiR_f ($R_f = CF_3$, C_2F_5) to give perfluoroalkylated products R–R_f [26]. Inspired by their work and based on our own experience with Me_3SiCF_2SPh (**1**) [27e], we envisioned that a similar fluoride ion-mediated nucleophilic fluoroalkylation of alkyl halides might be possible with reagent **1**, which could be used to prepare both $PhSCF_2$- and CF_2H-containing compounds. In this paper, we disclose our results on this study.

2. Results and discussion

First, we carried out the nucleophilic (phenylthio)difluoromethylation of ethyl iodide **2a** with Me_3SiCF_2SPh (**1**) [27] in the presence of a fluoride source. The reaction conditions

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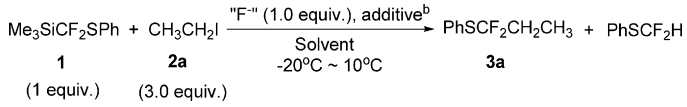
doi:10.1016/j.jfluchem.2008.01.010

Table 1
Optimization of the reaction conditions



Entry	"F⁻"	Solvent	Additive	Yield (%)[a]
1	TBAT	CH_2Cl_2	–	0
2	TBAT	DME	–	28
3	TBAT	DMF	–	0
4	KF	DME	–	0
5	CsF	CH_3CN	–	0
6	CsF	CH_2Cl_2	–	0
7	CsF	THF	–	21
8	CsF	DME	–	37
9	CsF	DME	18-Crown-6	32
10	CsF	DME	15-Crown-5	43
11	CsF	Diglyme	15-Crown-5	23
12	CsF	Et_2O	15-Crown-5	16
13	CsF	Toluene	15-Crown-5	20

[a]The yield was determined by ^{19}F NMR spectroscopy and GC–MS. [b]The molar ratio of **1/2a**/CsF/additive = 1:3:1:1.

were carefully tuned (see Table 1). It is apparent that the reaction was significantly influenced by both the fluoride source and the reaction solvent. When the reactions were carried out in DMF, CH_3CN, or CH_2Cl_2 solvent, and different fluoride sources [such as tetrabutylammonium triphenyldifluorosilicate (TBAT), KF, and CsF] were applied, no expected product **3a** was formed (Table 1, entries 1 and 3–6). In these cases, the only detectable fluorine-containing product was $PhSCF_2H$. After several trials, we found that the combination of 1,2-dimethoxyethane (DME) and CsF could give better results (entries 8–10), while reactions in THF, diglyme, Et_2O, and toluene resulted in lower yields (entries 7 and 11–13). Moreover, the addition of the crown ether to the reaction mixture was found to be beneficial, and 15-crown-5 gave better result than 18-crown-6 (entries 9 and 10).

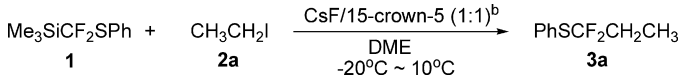
Further studies (see Table 2, entry 4) revealed that, when 2.0 equiv. of Me_3SiCF_2SPh (**1**) was used (relative to the amount of ethyl iodide **2a**), the yield of product **3a** was dramatically increased (93%). However, excess amount of ethyl iodide **2a** contributed little to the product yields, and the yield improvement was negligibly small even when 4.0 equivalent of ethyl iodide was applied (Table 2, entries 1–3). It is also worthwhile to mention that, no alkyl fluorides was detected as by-products in these reactions, which indicates that the rate of the reaction between ethyl iodide **2a** and CsF was much lower under the given reaction conditions.

Then we tried the less reactive electrophiles—ethyl bromide **4a** and ethyl chloride **5a**—to test their reaction with **1**/CsF/15-crown-5 under the optimized reaction conditions (as those for Table 2, entry 4). To our delight, when ethyl bromides **4a** was used as an electrophile, the reaction worked well and product **3a** was obtained in 85% isolated yield (see Scheme 1). Since alkyl bromides are relatively more available than alkyl iodides, it represents a practical advantage that alkyl bromides can be used in this reaction. However, when ethyl chloride was used, only trace amount of product **3a** was detected by ^{19}F NMR (Scheme 1).

We used the reaction conditions shown in Scheme 1 as the standard condition, and studied the scope of the reaction between reagent **1** and different alkyl bromides. The results are shown in Table 3. In all cases (phenylthio)difluoromethylated products **3** were obtained in good to excellent isolated yields, and the major detectable fluorine-containing by-product was $PhSCF_2H$.

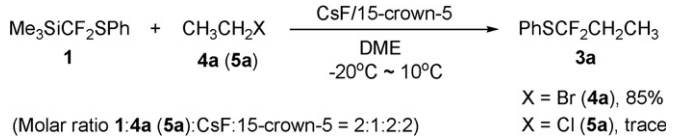
Products **3** are useful precursors for the preparation of difluoromethyl compounds. For instance, compound **3d** was treated with Bu_3SnH/AIBN in toluene at 90 °C, and the mixture was subject to a routine workup to afford difluoromethyl compound **6** in 95% yield (Scheme 2). Indeed, the present (phenylthio)difluoromethylation of primary alkyl bromides with **1** provides an alternative approach for the preparation of CF_2H-containing compounds, which were previously synthesized by using $PhSO_2CF_2H$ reagent under strongly basic conditions [13].

Table 2
Influence of the reactant ratio (**1/2a**) on the product yields



Entry	Molar ratio (**1/2a**)	Yield (%)[a]
1	1:1	42
2	1:3	43
3	1:4	47
4	2:1	93

[a]Isolated yield. [b]**1**/CsF/15-crown-5 = 1:1:1.

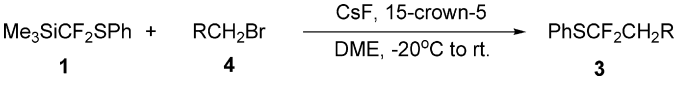


Scheme 1.

4.1. Typical procedure for the fluoride ion-mediated nucleophilic (phenylthio)difluoromethylation of alkyl halides

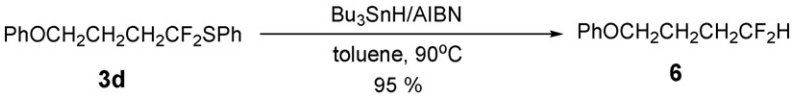
Under a nitrogen atmosphere, a mixture of dried CsF (182 mg, 1.2 mmol), 15-crown-5 (264 mg, 1.2 mmol), and freshly distilled DME (3.5 mL) was stirred for 5 min at −20 °C.

Table 3
Preparation of $PhSCF_2$-containing compounds **3** by fluoride-mediated substitution reactions between Me_3SiCF_2SPh (**1**) and alkyl bromides (**4**)



Entry[a]	Alkyl bromide	Product	Yield (%)[b]
1	CH_3CH_2Br (**4a**)	$CH_3CH_2CF_2SPh$ (**3a**)	85
2	$CH_3(CH_2)_5Br$ (**4b**)	$CH_3(CH_2)_5CF_2SPh$ (**3b**)	92
3	$PhCH_2Br$ (**4c**)	$PhCH_2CF_2SPh$ (**3c**)	88
4	$PhOCH_2CH_2CH_2Br$ (**4d**)	$PhOCH_2CH_2CH_2CF_2SPh$ (**3d**)	85
5	*p*-$CH_3C_6H_4OCH_2CH_2CH_2Br$ (**4e**)	*p*-$CH_3C_6H_4OCH_2CH_2CH_2CF_2SPh$ (**3e**)	94
6	*p*-$CH_3OC_6H_4OCH_2CH_2Br$ (**4f**)	*p*-$CH_3OC_6H_4OCH_2CH_2CF_2SPh$ (**3f**)	84

[a] Molar ratio **1/4**/CsF/15-crown-5 = 2:1:2:2.
[b] Isolated yield based on the amount of 4 that was used.



Scheme 2.

3. Conclusions

In conclusion, a facile and highly efficient nucleophilic (phenylthio)difluoromethylation of alkyl halides has been achieved via fluoride-mediated substitution reaction using [difluoro(phenylthio)methyl]trimethylsilane (Me_3SiCF_2SPh) reagent. The reaction proceeds well with primary alkyl bromides (or alkyl iodides) in DME solvent when CsF/15-crown-5 was used as the fluoride source/additive. The $PhSCF_2$-containing products can be readily transformed into CF_2H-containing compounds via a free-radical desulfurization method.

4. Experimental

Unless otherwise mentioned, solvents and reagents were purchased from commercial sources and used as received. DME was freshly distilled over sodium and stored under nitrogen atmosphere. Me_3SiCF_2SPh reagent was prepared according to the previous report [27a]. ^1H NMR spectra were recorded on a 300-MHz NMR spectrometer using Me_4Si as an internal standard. ^{19}F NMR spectra were recorded on a 300-MHz NMR spectrometer using $CFCl_3$ as an external standard. ^{13}C NMR spectra were recorded on a 500-MHz or a 400-MHz NMR spectrometer. Mass spectra were obtained on a HP5989A spectrometer. High-resolution mass data were recorded on a high-resolution mass spectrometer in the EI or MALDI mode.

Then a mixture of Me_3SiCF_2SPh (**1**) (280 mg, 1.2 mmol) and ethyl bromide (65 mg, 0.6 mmol) in DME (0.5 mL) was slowly added to the reaction flask. The reaction temperature was raised to 10 °C in 4 h, followed by adding H_2O (5 mL) to the reaction mixture. The solution mixture was extracted with Et_2O (15 mL 3×), and the combined organic phase was dried over $MgSO_4$. After the removal of volatile solvents under vacuum, the crude product was purified by silica gel column chromatography with petroleum ether to give product **3a** as an oily liquid, yield 85% (96 mg).

4.1.1. 1,1-Difluoropropyl phenyl sulfide (*3a*) ($CH_3CH_2CF_2SPh$)

Liquid; IR (film): 2987, 1477, 1442, 1227, 1174, 1140, 1027, 973 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.59–7.62 (m, 2H), 7.34–7.42 (m, 3H), 2.03–2.18 (m, 2H), 1.12 (t, J = 7.5 Hz, 3H); ^{19}F NMR ($CDCl_3$): δ −74.8 (t, J = 14.7 Hz, 2F); ^{13}C NMR ($CDCl_3$): δ 136.0, 130.4 (t, J = 276.6 Hz), 129.6, 129.0, 127.2, 32.1 (t, J = 24.5 Hz), 7.46 (t, J = 4.2 Hz); EI (*m*/*z* %) 188 (M^+, 37.7), 110 (100.0); HRMS (EI) calcd. For $C_9H_{10}F_2S$: 188.0471; found 188.0461.

4.1.2. 1,1-Difluoroheptyl phenyl sulfide (*3b*) ($CH_3(CH_2)_5CF_2SPh$)

Liquid; IR (film): 2959, 1475, 1442, 1172, 1042, 1025, 944 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.58–7.61 (m, 2H), 7.33–7.40 (m, 3H), 2.00–2.15 (m, 2H), 1.52–1.61 (m, 2H), 1.25–1.35 (m, 6H), 0.88 (t, J = 6.9 Hz); ^{19}F NMR ($CDCl_3$): δ −72.7 (t,

J = 14.6 Hz, 2F); ^{13}C NMR ($CDCl_3$): δ 136.1, 130.1 (t, J = 276.6 Hz), 129.6, 128.9, 127.3, 38.7 (t, J = 24.3 Hz), 31.4, 28.6, 23.0 (t, J = 6.2 Hz), 22.4, 14.0; EI (*m/z* %) 244 (M^+, 2.6), 110 (100.0); HRMS (EI) calcd. For $C_{13}H_{18}F_2S$: 244.1097; found 244.1102.

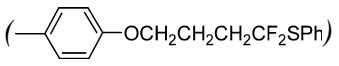
*4.1.3. 1,1-Difluoro-2-phenylethyl phenyl sulfide (**3c**) ($PhCH_2CF_2SPh$)*

Liquid; IR (film): 3066, 1498, 1475, 1442, 1224, 1155, 1031, 977 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.42–7.58 (m, 2H), 7.27–7.42 (m, 8H), 3.41 (t, J = 15.0 Hz, 2H); ^{19}F NMR ($CDCl_3$): δ −72.0 (t, J = 14.7 Hz, 2F); ^{13}C NMR ($CDCl_3$): δ 136.1, 131.9 (t, J = 3.8 Hz), 130.5, 129.6, 128.9, 128.6 (t, J = 277.9 Hz), 128.4, 127.7, 126.8, 45.1 (t, J = 23.9 Hz); EI (*m/z* %): 250 (M^+, 74.4), 110 (100.0); HRMS (EI) calcd. For $C_{14}H_{12}F_2S$: 250.0628; found 250.0636.

*4.1.4. 1,1-Difluoro-4-phenoxybutyl phenyl sulfide (**3d**) ($PhOCH_2CH_2CH_2CF_2SPh$)*

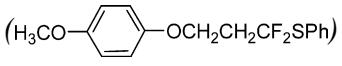
Liquid; IR (film): 3064, 1601, 1498, 1475, 1442, 1246, 1172, 1027, 972 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.59–7.62 (m, 2H), 7.23–7.46 (m, 5H), 6.85–7.23 (m, 3H), 3.98 (t, J = 6.3 Hz, 2H), 2.23–2.38 (m, 2H), 2.03–2.12 (m, 2H); ^{19}F NMR ($CDCl_3$): δ −73.1 (t, J = 14.6 Hz, 2F); ^{13}C NMR ($CDCl_3$): δ 158.7, 136.2, 130.0 (t, J = 277.1 Hz), 129.8, 129.5, 129.1, 127.0 (d, J = 3.5 Hz), 120.8, 114.5, 66.4, 35.5 (t, J = 23.3 Hz), 23.3 (t, J = 3.7 Hz); EI (*m/z* %) 294 (M^+, 7.5), 91 (100.0); HRMS (EI) calcd. For $C_{16}H_{16}F_2OS$: 294.0890; found 294.0904.

*4.1.5. 1,1-Difluoro-4-(p-tolyloxy)butyl phenyl sulfide (**3e**)*



Liquid; IR (film): 2872, 1614, 1585, 1513, 1475, 1442, 1244, 1174, 1025 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.62 (d, J = 7.5 Hz, 2H), 7.34–7.45 (m, 3H), 7.08 (d, J = 8.1 Hz, 2H), 6.78 (d, J = 7.8 Hz, 2H), 3.96 (t, J = 6.3 Hz, 2H), 2.28 (s, 3H), 2.23–2.38 (m, 2H), 2.02–2.12 (m, 2H); ^{19}F NMR ($CDCl_3$): δ −73.1 (t, J = 15.2 Hz, 2F);^{13}C NMR ($CDCl_3$): δ 156.6, 136.2, 130.1, 130.0 (t, J = 277.2 Hz), 129.9, 129.7, 129.0, 127.0 (d, J = 3.2 Hz), 114.4, 66.6, 35.5 (t, J = 23.3 Hz), 23.3 (t, J = 2.3 Hz), 20.5; EI (*m/z* %) 308 (M^+, 7.3), 91 (100.0); HRMS (EI) calcd. For $C_{17}H_{18}F_2OS$: 308.1046; found 308.1054.

*4.1.6. 1,1-Difluoro-3-(4′-methoxyphenoxy)propyl phenyl sulfide (**3f**)*



Liquid; IR (film): 1509, 1475, 1442, 1234, 1081, 1038, 827 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.62 (d, J = 6.6 Hz, 2H), 7.35–7.43 (m, 3H), 6.84–6.87 (m, 4H), 4.17 (t, J = 6.9 Hz, 2H), 3.76 (s, 3H), 2.56–2.66 (m, 2H); ^{19}F NMR ($CDCl_3$): δ −71.9 (t, J = 15.5 Hz, 2F); EI (*m/z* %) 310 (M^+, 25.1), 123 (100.0); HRMS (EI) calcd. For $C_{16}H_{16}F_2O_2S$: 310.0839; found 310.0843.

Acknowledgements

We gratefully acknowledge the National Natural Science Foundation of China (20502029, 20772144), Shanghai Rising-Star Program (06QA14063), and the Chinese Academy of Sciences (Hundreds-Talent Program and Knowledge Innovation Program) for financial support.

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