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Development of $PhSCF_2CF_2SiMe_3$ as a Tandem Anion and Radical Tetrafluoroethylene Equivalent: Preparation of Tetrafluoroethyl-Substituted Alcohols and Tetrafluorotetrahydropyrans

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Keywords: Fluorine / Alkylation / Nucleophilic addition / Radical reactions / Oxygen heterocycles

$PhSCF_2CF_2SiMe_3$ (**1**) was developed as a tandem anion and radical tetrafluoroethylene equivalent for the introduction of a CF_2CF_2 moiety. Fluoride-initiated nucleophilic additions of **1** to carbonyl compounds provide the corresponding alcohol adducts **2**. Reduction of **2** gives tetafluoroethyl-containing alcohols **3**, whereas 6-*exo* radical cyclizations of allyl ethers **4** yield tetrafluorotetrahydropyrans **5**.

Introduction

Fluoroorganic compounds display unique chemical, biological, and physical properties, which have proven useful in agricultural and medicinal chemistry and in materials science. In addition, the selective introduction of fluorine atom(s) or fluorine-containing moieties into organic molecules with the aim of positively influencing their biological properties is a powerful strategy in drug design.[1] Consequently, research into the development of new efficient reaction systems for selective fluorination or fluoroalkylation has been increasing.

In recent years, a number of novel methodologies have been reported for the introduction of fluoroalkyl moieties into organic molecules, and the introduction of perfluoroalkyl,[2] difluoromethyl, and difluoromethylene[3] groups has been extensively studied. In addition, incorporation of $H(CF_2)_n$– and –$(CF_2)_n$– groups, where $n > 2$, is straightforward by a nucleophilic or radical pathway, starting from halogenated precursors $H(CF_2)_nX$ and $X(CF_2)_nX$, respectively.[4] However, the introduction of tetrafluoroethyl (–CF_2CF_2H) and tetrafluoroethylene (–CF_2CF_2–) moieties is much more challenging. For example, the introduction of tetrafluoroethyl groups via tetrafluoroethyl radicals or carbanions generated from HCF_2CF_2X (X = Br, I, $SiMe_3$) is complicated by the lack of availability or high cost of halotetrafluoroethane precursors. Obvious candidates for the introduction of tetrafluoroethylene groups are 1,2-dihalotetrafluoroethanes: in fact, the Hu and Chen groups have reported successful radical chain reactions of 1,2-dihalotetrafluoroethanes with alkenes or alkynes.[5] Furthermore, Linclau and co-workers described the enantioselective synthesis of tetrafluorinated glucose and galactose derivatives, starting with radical addition of bromoiodotetrafluoroethane to an alkene.[6] In addition, the same group reported the enantioselective synthesis of several tetrafluoroethylene-containing monosaccharides, starting from commercially available $CH_2=CHCF_2CF_2Br$, which, after double-bond functionalization, underwent lithiation with MeLi and nucleophilic addition to the carbonyl group.[7] However, in contrast, organometallic species derived from 1,2-dihalotetrafluoroethanes suffer from facile β-halogen elimination to give tetrafluoroethylene.[8]

Other approaches towards tetrafluoroethylene-containing compounds, such as reaction of 1,2-dicarbonyls with SF_4/HF, employ highly toxic reagents and high pressure reaction conditions,[9] whereas reactions using the less aggressive Deoxofluor are limited to simple aromatic benzil derivatives.[10] Finally, the silylated derivatives $Me_3SiCF_2CF_2SiMe_3$[11] and $PhMe_2SiCF_2CF_2SiMe_2Ph$[12] undergo elimination of R_3SiF, thus acting as trifluorovinylation rather than tetrafluoroethylenation reagents.

Because of these limitations, there are currently no general methods available for the direct introduction of tetrafluoroethyl or tetrafluoroethylene moieties. Here we report our findings on the development of trimethyl(1,1,2,2-tetrafluoro-2-phenylsulfanylethyl)silane ($PhSCF_2CF_2SiMe_3$, **1**) as a tandem anion and radical tetrafluoroethylene synthon. Compound **1** features two types of difluoromethylene groups: a CF_2^- center, which can be obtained by activation of the silane (e.g., using fluoride ions), and a $CF_2^{\cdot}$ center, which can be formed by homolytic cleavage of the C–S bond under free radical conditions. This design should circumvent the above-mentioned β-fluoride elimination problem, enabling preparation of selectively substituted tetrafluoroethylene-containing compounds through the orthogo-

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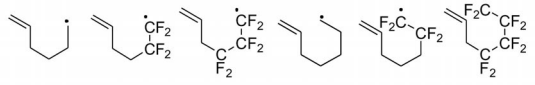
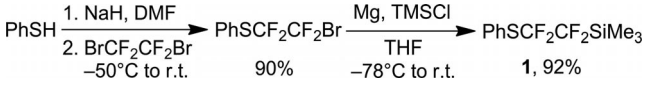
nal reactivities of fluorinated carbanion and radical centers. Compound **1** can be viewed as an extension of $PhSCF_2SiMe_3$, which was successfully used as a nucleophilic (phenylthio)difluoromethylenation reagent of carbonyl compounds[13] or difluoromethylene radical anion equivalent, through nucleophilic addition to sulfinyl imines[14] or cyclic imides,[15] followed by radical cyclizations. In the present study, we addressed the proposed reactivity of compound **1** by investigating nucleophilic addition to carbonyl compounds, followed by either reductive cleavage of the phenylsulfanyl group, to give a tetrafluoroethyl-containing alcohol, or radical cyclization to yield a tetrafluorotetrahydropyran: neither compound has been previously reported [except for compound **3a** (vide supra)]. 6-*exo*-Cyclizations of tetrafluoro-6-heptenyl ether radicals to tetrafluorotetrahydropyrans should be feasible and fast. A systematic study by Dolbier Jr. and co-workers demonstrated that fluorine substitution at the radical center is associated with a remarkable rate enhancement effect in 5-*exo*, 6-*exo*, and 6-*endo* cyclizations (Table 1).[16] For example, 6-*exo* cyclizations of tetra- and octafluoroheptenyl radicals occur with rate constants that are three orders of magnitude larger than those observed for their hydrocarbon analogues.

Table 1. Cyclization reactivities of hydrocarbon and hydrofluorocarbon radicals at 25 °C.[16]

						
$k_{5\text{-}exo}$ [s^{-1}]	2.7×10^5	1.2×10^7	4.5×10^7			
$k_{6\text{-}exo}$ [s^{-1}]				5.4×10^3	1.4×10^7	2.0×10^7
$k_{6\text{-}endo}$ [s^{-1}]	5.0×10^3		5.6×10^6			

Results and Discussion

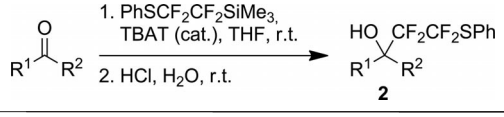
Silane **1** was prepared in excellent yield as described previously[17] by using a two-step reaction starting from thiophenol and 1,2-dibromotetrafluoroethane[18] (Scheme 1). The use of compound **1** was previously reported for the preparation of sulfonyl fluorides and lithium sulfonates, which have potential applications as electrolytes in lithium batteries.[17]



Scheme 1. Synthesis of compound **1** from 1,2-dibromotetrafluoroethane.

Nucleophilic addition of **1** to aldehydes and ketones was investigated (Table 2). Reaction with benzaldehyde proceeded smoothly in the presence of a twofold excess of **1** and catalytic amounts of fluoride initiator (TBAT[19]/THF or CsF/DMF) at ambient temperature, giving the adduct as a TMS-ether, which after silyl group removal using aqueous hydrochloric acid gave **2a** in excellent yield (Table 2, Entry 1). The TBAT/THF system was preferred for other substrates because of easier product isolation, whereas the use of an excess amount of **1** improved product conversion ($PhSCF_2CF_2H$ was identified as a byproduct). Aromatic aldehydes with either electron-withdrawing or electron-donating groups worked equally well, whereas good yields of adducts **2** were also obtained starting from aliphatic aldehydes. In contrast, the reactivity of simple ketones was significantly reduced. For example, acetophenone gave only 36% of the corresponding **2h** (Table 2, Entry 8). Efforts to increase the product yield, by employing other, less sterically demanding initiators (CsF, nBu$_4$NF, Me$_4$NF), were not successful. Furthermore, only trace amounts of the product were formed from cyclohexanone, (Table 2, Entry 9). Interestingly, the use of trifluoroacetophenone resulted in the formation of a TMS-ether adduct that is resistant to HCl cleavage; however, aqueous HF gave **2j** in excellent yield (Table 2, Entry 10), suggesting that the lack of reactivity of simple ketones is due to their low electrophilicity rather than steric reasons.

Table 2. Preparation of adducts **2** by fluoride-initiated nucleophilic addition of **1** to carbonyl compounds.[a]



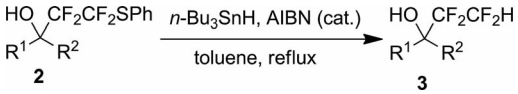
Entry	R^1	R^2	**2**, Yield [%][b]
1	Ph	H	**2a**, 91
2	4-ClC_6H_4	H	**2b**, 93
3	4-$MeOC_6H_4$	H	**2c**, 86
4	1-naphthyl	H	**2d**, 80
5	2-naphthyl	H	**2e**, 75
6	n-C_6H_{13}	H	**2f**, 72
7	$PhCH_2CH_2$	H	**2g**, 86
8	Ph	Me	**2h**, 36
9	–$(CH_2)_5$–		**2i**, trace
10	Ph	CF_3	**2j**, 91[c]

[a] Reactions were performed with carbonyl compound (2 mmol), **1** (4 mmol, 2.0 equiv.), and TBAT (1 mol-%) in THF (8 mL) at room temperature for 1 h, followed by addition of HCl (3 mL, 1 M) at room temperature for 1 h. [b] Isolated yield. [c] HF (4 mL, 1 M) was used instead of HCl.

Following synthesis of adducts **2**, reductive cleavage of the phenylsulfanyl (PhS) group was investigated. The PhS group was readily substituted with hydrogen by using an excess amount of nBu$_3$SnH and a catalytic amount of AIBN in refluxing toluene, giving the corresponding tetrafluoroethyl-containing secondary or tertiary alcohols in good to high yields (Table 3).

Next, we investigated intramolecular trapping of the tetrafluoroethyl radical intermediate, generated by carbon–sulfur bond cleavage by an unsaturated functional moiety. For this purpose, allyl ether **4a** was synthesized. Using reaction conditions similar to those employed for the formation of compounds **3**, allyl ether **4a** was subjected to 6-*exo* radical cyclization to give tetrafluorotetrahydropyran **5a** in moderate yield (Table 4, Entry 1).

Table 3. Preparation of alcohols **3** by reductive cleavage of adducts **2**.[a]



Entry	**2**	R^1	R^2	**3**, Yield [%][b]
1	**2a**	Ph	H	**3a**, 77
2	**2b**	4-ClC_6H_4	H	**3b**, 98
3	**2c**	4-$MeOC_6H_4$	H	**3c**, 80
4	**2d**	1-naphthyl	H	**3d**, 65[c]
5	**2e**	2-naphthyl	H	**3e**, 84
6	**2f**	*n*-C_6H_{13}	H	**3f**, 92
7	**2g**	$PhCH_2CH_2$	H	**3g**, 92
8	**2h**	Ph	Me	**3h**, 89

[a] Reactions were conducted using **2** (1 mmol), nBu_3SnH (1.75 mmol, 1.75 equiv.), and AIBN (0.15 mol, 0.15 equiv.) in toluene (8 mL) under reflux for 4 h. [b] Isolated yield. [c] Reaction time was 15 h.

Formation of side product **6a** was suppressed by slow addition of nBu_3SnH and AIBN. Compound **5a** was formed as a mixture of *trans* and *cis* isomers in an 82:12 ratio. A single *trans*-**5a** was obtained by crystallization from *n*-hexane, and its relative stereochemistry was determined by X-ray crystallography (Figure 1).[20] A series of tetrafluorotetrahydropyran derivatives **5b**–**k** was synthesized as a mixtures of isomers in moderate to good yields by radical cyclization of adducts **4b**–**k**. Based on X-ray crystallographic analysis of the major *trans*-isomer of **5a** and comparison of the ^{19}F NMR spectra of *trans*-**5a** and *cis*-**5a**, we established that the *trans* isomers of **5b**–**g** were the major isomers, and that the *trans*/*cis* ratio ranged from 76:24 to 89:11 (determined by ^1H NMR spectroscopy and confirmed by ^{19}F NMR spectroscopy). Benzyl-substituted product of cyclization **5k** was formed in a 79:21 ratio, which was determined by GC–MS analysis rather than NMR spectroscopy, as both the mixture of isomers of **5k** and the pure major isomer obtained by crystallization from *n*-hexane displayed identical NMR spectra (see Supporting Information for GC–MS and NMR spectroscopic data). The major isomer of **5k** was thus presumed to be a *trans* isomer by analogy.

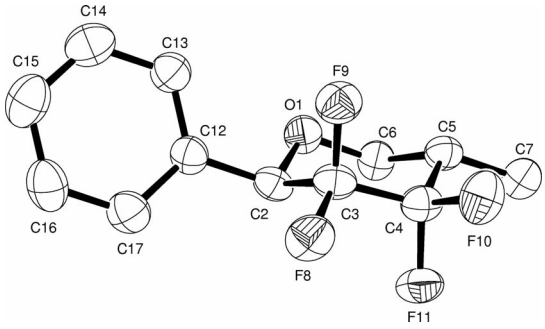
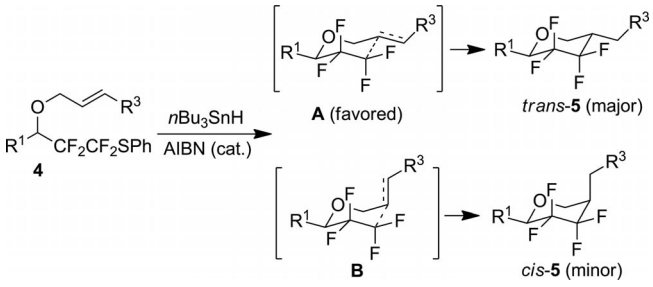


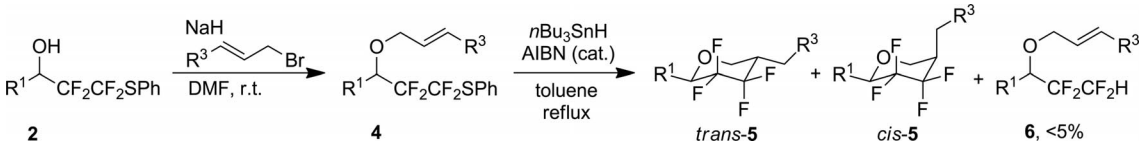
Figure 1. X-ray crystal structure of the major isomer of **5a**. Hydrogen atoms are omitted for clarity and thermal ellipsoids are set at 50% probability.

The stereochemistry assumed by compounds **5** can be rationalized as shown in Scheme 2, where radical-mediated cyclization proceeds through a 6-*exo*-*trig* cyclization mode. Transition state **A**, which leads to *trans*-**5**, should be ener-



Scheme 2. Proposed transition states for 6-*exo* radical cyclizations of **4** to **5**.

Table 4. Formation of allyl ethers **4**[a] and radical cyclization to tetrafluorotetrahydropyrans **5**.[b]



Entry	**2**	R^1	R^3	**4**, Yield [%][c]	**5**, Yield [%][c]	**5**, *trans*/*cis*[d]
1	**2a**	Ph	H	**4a**, 90	**5a**, 53	82:18
2	**2b**	4-ClC_6H_4	H	**4b**, 77[e]	**5b**, 60	86:14
3	**2c**	4-$MeOC_6H_4$	H	**4c**, 81	**5c**, 62	89:11
4	**2e**	2-naphthyl	H	**4e**, 59	**5e**, 74	84:16
5	**2f**	*n*-C_6H_{13}	H	**4f**, 77	**5f**, 61	77:23
6	**2g**	$PhCH_2CH_2$	H	**4g**, 83	**5g**, 84	76:24
7	**2a**	Ph	Ph	**4k**, 91	**5k**, 67	79:21[f]

[a] Reactions were conducted using **2** (1 mmol), NaH (2 mmol), and $R^3CH{=}CHCH_2Br$ (3 mmol) in THF (5 mL) at room temperature for 2 h. [b] Reactions were performed by addition of nBu_3SnH (1.75 mmol) and AIBN (0.15 mmol) in toluene (5 mL) over 3 h (using a syringe pump) to a refluxing solution of **4** (1 mmol) in toluene (3 mL) followed by reflux for 1 h. [c] Isolated yield. [d] Determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. [e] Reaction time was 4 h. [f] Determined by GC–MS analysis of the crude reaction mixture.

getically more favorable than transition state **B** for the *cis*-**5** because it does not involve unfavorable 1,3-diaxial interactions between the fluorine atom and the CHR^3 group.

Conclusions

In conclusion, we have developed $PhSCF_2CF_2SiMe_3$ (**1**) as a tandem anion and radical tetrafluoroethylene equivalent for introduction of $–CF_2CF_2H$ and $–CF_2CF_2–$ moieties. Compound **1** underwent fluoride-initiated nucleophilic addition to aldehydes and activated ketones, providing (after hydrolysis of the intermediate TMS-ether) substituted 2,2,3,3-tetrafluoro-3-phenylsulfanylpropan-1-ols (**2**) in high yields. Compounds **2** underwent reduction under free radical conditions to substituted 2,2,3,3-tetrafluoropropan-1-ols (**3**) in moderate to high yields, demonstrating the application of **1** as a tetrafluoroethyl carbanion equivalent. Compounds **2** were converted into allyl ethers **4** and cyclized under free radical conditions to give substituted tetrafluorotetrahydrofurans **5** in a 76:24 to 89:11 *trans*/*cis* ratio in moderate to good yields.

Supporting Information (see footnote on the first page of this article): Full characterization and copies of the ^1H, ^{13}C, and ^{19}F NMR spectra of compounds **3**–**5**.

Acknowledgments

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[18] Also known as R-114B2 or Halon 2402, a dense (d = 2.18 g cm^{-3}), volatile (b.p. 47 °C), colorless liquid, which is used in fire suppression systems, mainly in military land vehicles, naval vessels, and aircrafts. Large-scale production of Halon 2402 has been banned since 1994 in accordance with obligations under the Montreal Protocol on Substances that Deplete the Ozone Layer. However, the compound is still commercially available for research purposes, and multikilogram quantities can be obtained from specialized Halon 2402 storage facilities.

[19] Tetrabutylammonium triphenyldifluorosilicate.

[20] CCDC-824772 (for **5a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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