ORGANIC
LETTERS

2013
Vol. 15, No. 22
5666–5669

Electrophilic Difluoro(phenylthio)methylation: Generation, Stability, and Reactivity of α-Fluorocarbocations

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Received September 13, 2013

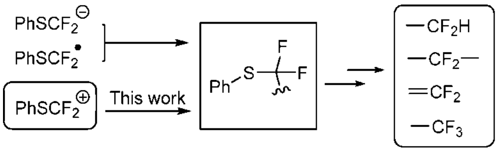
ABSTRACT

Electrophilic difluoro(phenylthio)methylation of allylsilanes has been achieved using bromodifluoro(phenylthio)methane ($PhSCF_2Br$) and silver hexafluoroantimonate ($AgSbF_6$). The structural assignment and observation of α-fluorocarbocation were substantiated by NMR and theoretical calculations. Detailed mechanistic and electronic studies have provided a fundamental understanding of the reactivity and stability of the difluoro(phenylthio)methylium cation ($PhSCF_2^+$).

Organofluorine compounds have attracted considerable interest over the past decade finding numerous applications in pharmaceuticals, agrochemicals, and materials science.[1] Consequently, there has been a rapid increase in the development of new synthetic methodologies and reagents for the selective incorporation of fluorine atoms or fluoroalkyl groups into organic molecules.[2]

Fluorinated organosulfur reagents have attracted this high level of interest as they provide organic chemists access to multiple synthetic targets from fluorinated sulfoxide, sulfone, and sulfide reagents.[3] In particular, the introduction of a difluoro(phenylthio)methane ($-CF_2SPh$) moiety into organic molecules has proven to be a highly versatile building block for the selective incorporation of difluoromethane ($-CF_2H$), difluoroalkane ($-CF_2-$), difluoromethylene ($=CF_2$), and trifluoromethane ($-CF_3$) moieties (eq 1).[4]

Methodologies for nucleophilic (and, to a lesser extent, radical) difluoro(phenylthio)methylation have been studied comprehensively.[4b,5] To the best of our knowledge there has been no report of electrophilic difluoro(phenylthio)methylation.



(1)

Currently there is only one hypervalent iodine(III)–CF_2SO_2Ph reagent developed by Hu capable of electrophilic difluoro(phenylsulfonyl)methylation toward S-nucleophiles or α,*β*- and *β*,*γ*-unsaturated carboxylic acids, the latter of which utilizes a copper(II) catalyst.[6]

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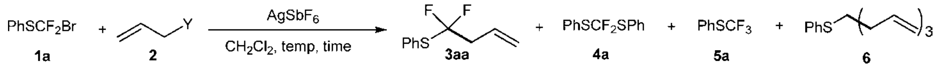
10.1021/ol402631t

Table 1. Optimization of Conditions for Electrophilic Difluoro(phenylthio)methylation of Allyltrimethylsilane and Allyltributyltin with Bromodifluoro(phenylthio)methane[a]



entry	2 (equiv)	Y	$AgSbF_6$ (equiv)	temp (°C)	time (h)	conv (%)	yield (%)[b] **3aa**	**4a**	**5a**	**6**
1[c]	1.5	$SnBu_3$	1.15	−42 to rt	2	100	–	–	64	–
2[d]	1.5	$SnBu_3$	1.15	−42 to rt	2	100	–	–	56	–
3	2.5	$SnBu_3$	1.15	−78 to rt	3	64	3	–	–	57
4	2.5	$SiMe_3$	1.15	−78 to rt	3	69	5	–	–	52
5	1.1	$SnBu_3$	1.05	−42	1	46	10	14	–	2
6	1.1	$SnBu_3$	1.3	−61	2	74	34	16	–	–
7	1.1	$SnBu_3$	1.8	−61	0.5	98	38	19	–	–
8	1.1	$SnBu_3$	2	−78	0.5	100	43	21	–	–
9	1.1	$SnBu_3$	2	−94	1	100	46	22	–	–
10	1.1	$SiMe_3$	2	−78	0.5	100	70	23	–	–
11[e]	1.1	$SiMe_3$	2	−78	0.5	100	94	5	–	–
12[e]	1.1	$SnBu_3$	2	−78	0.5	100	56	38	–	–

[a] Reaction conditions for entries 3–10: A solution of $AgSbF_6$ in DCM (5 mL) was added dropwise over 15 min to a mixture of **1a** (0.5 mmol) and **2** in DCM (5 mL). [b] Isolated yields based on **1a**. [c] **1a** in DCM was added dropwise to $AgSbF_6$ in DCM followed by addition of **2**. [d] A solution of **1a** and **2** in DCM was added dropwise to $AgSbF_6$ in DCM. [e] $AgSbF_6$ in DCM and **1a** in DCM in separate flasks were added simultaneously to **2** in DCM.

Pioneering work on fluorinated carbocations has revealed fluorine's unique ability to stabilize carbocations.[7] Utilizing the strong Lewis acid antimony pentafluoride (SbF_5) with HF, FSO_3H, SO_2, or SO_2ClF as solvents rapidly became the method of choice for generating and characterizing stable fluorinated carbocations by means of NMR spectroscopy and X-ray diffraction.[8] Despite the discovery of numerous well characterized α-fluorocarbocations, their synthetic utility has remained limited due to the harsh conditions required for the generation, often resulting in nonfluorinated products.[9]

Our previous effort to generate and utilize the difluoro(phenylthio)methylium cation (**1a-cation**) by extensive screening with strong Lewis acids in the presence of activated aromatics or heteroaromatics resulted in the loss of fluorine and isolation of thioester products, while mild Lewis acids failed to react with **1a**.[9a] Inspired by the use of SbF_5 we envisioned silver hexafluoroantimonate ($AgSbF_6$) as a selective Lewis acid toward silver(I) assisted abstraction of bromine from bromodifluoro(phenylthio)methane (**1a**), while providing SbF_6^- as a suitable stabilizing counteranion.[10]

Initial attempts to generate and trap the **1a-cation** indicated the reaction was highly dependent on the order of addition of reagents. Unexpectedly, when the **1a-cation** was generated in the presence of excess $AgSbF_6$, trifluoro(phenylthio)methane $PhSCF_3$ (**5a**) was isolated (Table 1, entries 1 and 2) suggesting the **1a-cation** was trapped by the fluoride anion from SbF_6^-.[11] Indeed, in generating the **1a-cation** in the presence of allyltrimethylsilane (**2**) or allyltributyltin by adding $AgSbF_6$ to a mixture of **1a** and **2**, a trace amount of the desired product **3aa** was isolated with **6** as the major product (entries 3 and 4). It was crucial to quench the reaction below −61 °C to prevent ionization of **3aa** leading to the loss of fluorine and formation of **6**, as excess $AgSbF_6$ (2 equiv) was required for complete conversion of the starting material **1a** (entries 4–8). Interestingly, when $AgSbF_6$ was added to **1a** and **2**, **1a** behaved as a competitive S-nucleophile resulting in the isolation of difluorobis(phenylthio)methane (**4a**). After extensive experimentation it was found that to suppress the formation of product **4a**, simultaneous addition of **1a** and $AgSbF_6$ to **2** resulted in an excellent yield of the desired product **3aa** (entry 11). Under optimized conditions using allyltrimethylsilane as a substrate, allyltributyltin provided an inferior yield of the desired product **3aa** (entry 12). We therefore focused our attention on allyltrimethylsilanes for exploring the scope of the reaction.

Under optimized conditions (Table 1, entry 11), various functionalized allyltrimethylsilanes were evaluated toward electrophilic difluoro(phenylthio)methylation (Scheme 1). Allyltrimethylsilanes without nucleophilic functional groups provided the corresponding products in good yields.

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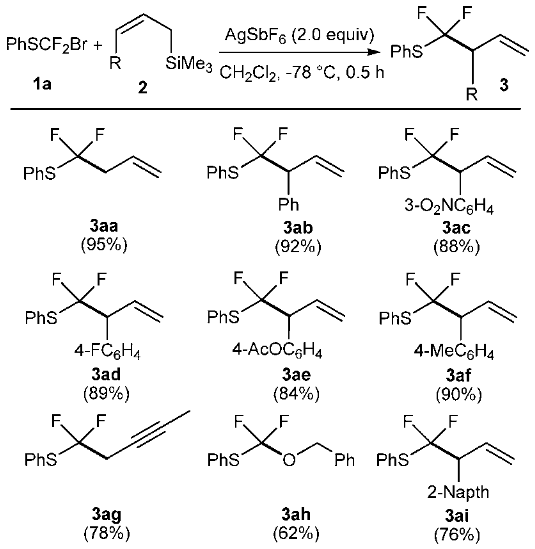
Scheme 1. Electrophilic Difluoro(phenylthio)methylation of Allyltrimethylsilanes **2**[a]

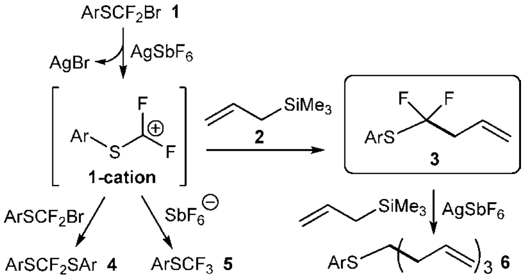


[a] Yield of isolated product. General procedure: AgSbF$_6$/DCM (0.2 M) and PhSCF$_2$Br/DCM (0.1 M) were added simultaneously to trimethylallylsilane **2**/DCM (0.18 M) over 5 min at −78 °C.

The use of 3-(trimethylsilyl)-1,2-butadiene, an allene substrate, as a nucleophile provided the corresponding alkyne product **3ag** in good yield. Interestingly, when (4-(benzyloxy)but-2-enyl)trimethylsilane was used as a substrate the major product **3ah** resulted from ε attack of the oxygen atom and subsequent loss of butadiene. Despite the high yield of the selected examples the substrate scope remains limited due to the reactivity and soft electrophilic nature of the α-fluorocarbocation. Less reactive carbon nucleophiles (vinyltributyltin, toluene, 1,4-dimethoxybenzene) were briefly investigated under optimized conditions, but did not provide any of the corresponding products resulting in **4a** exclusively and the recovery of the nucleophile. In dichloromethane, AgSbF$_6$ is a strong oxidant rendering otherwise promising nucleophiles incompatible (1,2,4-trimethoxybenzene and trimethylsilyl enol ethers) as oxidative homocoupling predominates. Other soft carbon nucleophiles including copper, silver, lithium, and zinc phenylacetylides were briefly investigated, but only products **4a** and **5a** were isolated.

In an effort to expand the substrate scope we investigated the use of milder silver salts (silver triflate, silver trifluoroacetate, silver tetrafluoroborate, and silver *p*-toluenesulfonate) with allyltrimethylsilane, but without success. Instead, silver tetrafluoroborate led to the isolation of **5a** via abstraction of fluoride from BF$_4^-$, whereas silver *p*-toluenesulfonate resulted in the isolation of difluoro(phenylthio)methyl *p*-tolenesulfonate (**7** in Supporting Information (SI)). These results provide further evidence for the high electrophilicity of **1a-cation**.

Scheme 2. Proposed Reaction Mechanism



To exclude the possibility of a radical or single electron transfer (SET) process we performed a series of probing experiments (Table S4).[12] Visible light (radical initiator) had little influence on the yield of product **3aa** (67% vs 62% in the dark). The addition of 1,4-dinitrobenzene (radical inhibitor) had negligible impact on the product yield (42%). Surprisingly, 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT) behaved as a C-nucleophile via oxidative addition leading to 2,6-di-*tert*-butyl-4-(difluoro-(phenylthiomethyl)-4-methylcyclohexa-2,5-dienone (**8** in SI) in good yield (72%), presumably through an electrophilic process, as PhSCF$_2$H was not detected in the crude reaction mixture. Moreover, the addition of AIBN and *p*-Me-styrene (radical scavengers) had negligible impact on the product yield (57% and 42% respectively), whereas TEMPO proved to be incompatible with AgSbF$_6$ resulting in the oxidation of TEMPO and precipitation of Ag^0.[13] We have previously demonstrated the generation of the difluoro(phenylthio)methyl radical is effectively trapped with styrene, thus it is most important to note radical trapped products were not detected in crude ^{19}F NMR for all additives.[4b] On the basis of these experiments we propose the mechanism proceeds exclusively through the difluoro(phenylthio)methylium cation (Scheme 2).

Intrigued by the unusual reactivity of **1a-cation** we investigated the electronic effect of sulfur oxidation and substitution on the phenyl ring on the generation and stability of the **1-cation** (Table 2). The use of sulfoxide and sulfone (**1b** and **1c**) resulted in the recovery of starting material highlighting the importance of the sulfur lone pair aiding in the ionization of bromine. Substitution of fluorine in the para position had negligible impact whereas the inductive withdrawing and resonance donating properties of chlorine and bromine resulted in a decreased yield. Methoxy as an electron donating group (**1g**) led to the increased yield of **4g** presumably from the increased nucleophilicity of the sulfur atom. Additionally, the aromatic ring of **3ga** became activated toward electrophilic aromatic substitution, trapping a second 4-CH$_3$OC$_6$H$_4$SCF$_2$– moiety (**9** in SI). Strong electron withdrawing groups (**1h** and **1i**) resulted in the recovery of starting material.

To further investigate the electrophilic nature of this reaction we attempted to characterize the **1a-cation** via

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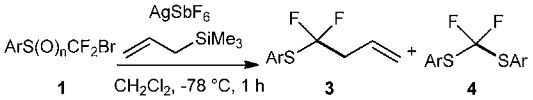
low temperature ^{19}F and ^{13}C NMR. Initial results using $PhSCF_2Br$ (**1a**) at −50 °C indicated the **1a-cation** was immediately trapped with a fluoride ion forming **5a** and $Sb_2F_{11}^-$.[14] The poorly nucleophilic SbF_6^- anion has been previously demonstrated to provide fluoride in the presence of extremely electrophilic species such as the trifluoromethyl cation (CF_3^+), driven by the formation of the strong C−F bond in the resulting tetrafluoromethane (CF_4).[15] Consistent with these findings, we propose that abstraction of fluoride from SbF_6^- by $PhSCF_2^+$ results in thermally stable $PhSCF_3$ with an additional driving force attributed to the polymerization of SbF_5/SbF_6^-.[16] Additional evidence was obtained when attempting to trap $PhSCF_2^+$ with 4-dimethylaminopyridine (DMAP) resulting in the isolation of $PhSCF_3$ (**5a**) and precipitation of a DMAP/$Sb_2F_{11}\cdot SbF_5$ complex containing protonated DMAP, $[Sb_2F_{11}]^-$, and SbF_5 moieties as confirmed by single crystal X-ray diffraction (see SI).

In anticipation of stabilizing the cation, we employed bromodifluoro(4-methoxyphenylthio)methane (**1g**) as a substrate. After mixing **1g** with $AgSbF_6$ for 10 min at −78 °C, a ^{19}F chemical shift at $\delta_F = +45.2$ ppm (Δ^{19}F 68.2) and ^{13}C chemical shift at $\delta_C = +234.4$ ppm (Δ^{13}C 114.6) as an apparent doublet ($^1J_{CF} = 390$ Hz) were observed at −60 °C. The downfield shifts of the fluorine and carbon signals suggested the formation of α-fluorocarbocation intermediates, which can be the α-difluorocarbocation $[(4\text{-}CH_3OC_6H_4S)CF_2]^+$, **1g-cation**, or α-monofluorocarbocation $[(4\text{-}CH_3OC_6H_4S)_2CF]^+$, **4g-cation**, generated by self-attack of **1g**. Combined theoretical and experimental ^{19}F and ^{13}C NMR chemical shifts can give additional support for structure identification.[8e,17] Thus, to identify the α-fluorocarbocation intermediate observed in this work, we performed density functional calculations for the ^{19}F and ^{13}C chemical shifts of **1a**, the **1g-cation**, the **4g-cation**, and several other fluoro compounds with available experimental chemical shifts (**10**−**12**) (Figure S1 and Table S2).

The calculated ^{19}F chemical shift of the **1g-cation** could be observed at an average of +34 ppm while the calculated ^{19}F chemical shift of the **4g-cation** is at +38.9 ppm (Figure S1). Within the calculation error, the presence of the **4g-cation** is more likely for the experimentally observed value at +45.2 ppm. Moreover, the calculated ^{13}C chemical shift of the carbocation center in the **4g-cation** (+222.2 ppm) is in better agreement with the experiment (+234.4 ppm) than that in the **1g-cation** (+169.3 ppm). The more electron shielded ^{13}C NMR shift of **1g-cation** indicates fluorine plays a more prominent role to stabilize the carbocation center. Indeed, optimized geometries of the **1g-cation** and **4g-cation** showed that the C−F bond distance in the **1g-cation** (1.29 Å) is relatively shorter than that of the **4g-cation** (1.33 Å) (Figure S1), suggesting a higher extent of p(π) back bonding from fluorine to the carbocation center.[15]

Table 2. Electronic Effect on the Generation and Stability of the Difluoro(phenylthio)methylium Cation[a]



substrate	Ar	*n*	yield (%)[b]			
1a	C_6H_5	0	**3aa**	65 (61)	**4a**	18 (16)
1b	C_6H_5	1		no reaction		
1c	C_6H_5	2		no reaction		
1d	$4\text{-}FC_6H_4$	0	**3da**	71 (60)	**4d**	20 (18)
1e	$4\text{-}ClC_6H_4$	0	**3ea**	47	**4e**	18
1f	$4\text{-}BrC_6H_4$	0	**3fa**	17	**4f**	15
1g	$4\text{-}CH_3OC_6H_4$	0	**3ga**	50 (48)	**4g**	30 (25)
1h	$4\text{-}O_2NC_6H_4$	0		no reaction		
1i	$2,4\text{-}F_2C_6H_4$	0		no reaction		

[a] Reaction conditions: A solution of $AgSbF_6$ (1 mmol) in DCM (10 mL) was added dropwise over 5 min to a mixture of **1a**−**i** (0.5 mmol) and allyltrimethylsilane **2** (0.6 mmol) in DCM (5 mL). [b] Yields were determined by ^{19}F NMR using $PhSCF_2SO_2Ph$ as an internal standard; yields in parentheses are of isolated products.

To estimate the stability of the **4g-cation** vs the **1g-cation**, we calculated solvent corrected relative free energies for the fluoride transfer reactions (Figure S2). The fluoride transfer from $[SbF_6]^-$ to the **1g-cation**, to form $4\text{-}CH_3OC_6H_4SCF_3$ (**5g**), is slightly exergonic (−2.29 kcal/mol) while the same reaction to **4g-cation** is unfavorable (+17.94 kcal/mol); that is **1g-cation**, once formed, is more reactive than **4g-cation**. Thus, we concluded that the experimentally observed α-fluorocarbocation is the **4g-cation**.

In summary we have developed for the first time the direct method for electrophilic difluoro(phenylthio)methylation of α-difluorocarbocations with carbon nucleophiles. The chemical and theoretical evidence for the presence of the difluoro(phenylthio)methylium cation was also provided. The studies also revealed that the α-difluorocarbocation is a very reactive species which could be trapped at low temperature. Further application of this chemistry is under investigation.

Acknowledgment. We thank the Center of Excellence for Innovation in Chemistry (PERCH-CIC), the Office of the Higher Education Commission, and Mahidol University under the National Research Universities Program of Thailand for financial support.

Supporting Information Available. Experimental, crystallographic, computaional details, and Cartesian coordinate of all calculated structures. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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