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An Unconventional Mechanistic Insight into SCF_3 Formation from Difluorocarbene: Preparation of ^{18}F-Labeled α-SCF_3 Carbonyl Compounds

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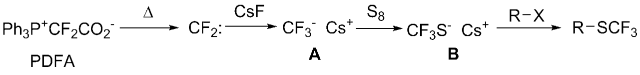
Abstract: *Trifluoromethylthiolation by sulfuration of difluorocarbene with elemental sulfur is described for the first time, which overrides long-standing trifluoromethyl anion-based theory. Mechanistic elucidation reveals an unprecedented chemical process for the formation of thiocarbonyl fluoride and also enables transition-metal-mediated trifluoromethylthiolation and [^{18}F]trifluoromethylthiolation of α-bromo carbonyl compounds with broad substrate scope and compatibility.*

Over the past several decades, there have been significant advances in the chemistry of difluorocarbene, which is a valuable and versatile intermediate for organic synthesis and particularly for fluorine incorporation.[1] As a singlet carbene,[2] and the most stable dihalocarbene,[1d] difluorocarbene shows moderate electrophilicity because of a strong inductive effect and an electron-donating resonance effect induced by fluorine. Understanding of difluorocarbene reactivity has led to development of a variety of novel organic transformations,[1] including difluoromethylation,[3] trifluoromethylation,[4] and [2+1] cycloaddition.[3a] We recently discovered a difluorocarbene-derived one-step [^{18}F]-trifluoromethylthiolation method,[5] which is one of the first examples[5,6] of its type despite significant progress with the non-radioactive version of the transformation. While we have demonstrated the novelty and utility of difluorocarbene in [^{18}F]trifluoromethylthiolation, the characteristics of these radiofluorination reactions—including the underlying mechanism and interaction with transition metals—remain elusive and present a major roadblock to further advancement of these reactions in radiolabeling of SCF_3-containing pharmaceuticals such as Cefazaflur.

Herein, we report an unprecedented mechanistic observation of trifluoromethylthio formation from difluorocarbene, sulfur, and fluoride, and the subsequent interactions between the generated SCF_3 anions and transition metals. Supported by experimental and theoretical studies, this work overrides our putative and long-standing interpretation of trifluoromethylthio group formation from difluorocarbene and has lead us to discover a new class of trifluoromethylthiolation for α-bromo carbonyl compounds in the presence of a copper complex. As a proof of concept, we demonstrate a general and practical copper-mediated radiosynthesis of ^{18}F-labeled SCF_3 carbonyl compounds with broad substrate scope and functional group compatibility, which is otherwise hardly achievable by traditional methods.

Difluoromethylene phosphobetaine $Ph_3P^+CF_2CO_2^-$ (PDFA), first developed by us[4i,j,5,7] and utilized by other groups,[4k,8] was found to be an efficient difluorocarbene agent for one-step trifluoromethylthiolation.[5] On the basis of several known reports showing that trifluoromethyl anion is formed from difluorocarbene[9] and reacts with elemental sulfur to give trifluoromethylthio anion,[10] we originally postulated that difluorocarbene generated in situ from PDFA might be readily trapped by fluoride to produce trifluoromethyl anion **A**, which reacts with elemental sulfur to give trifluoromethylthio anion **B** and eventually yields SCF_3 products (Scheme 1).[5]

However, further studies on the process indicated an unconventional mechanistic pathway for trifluoromethylthiolation. Specifically, difluorocarbene may undergo sulfuration with elemental sulfur to afford thiocarbonyl fluoride ($S{=}CF_2$) instead of being trapped by fluoride to give CF_3^- anion **A**. If anion **A** were generated during the reactions, the presence of water in the reaction system would lead to a rapid and irreversible formation of trifluoromethane



Scheme 1. Originally proposed mechanism for trifluoromethylthiolation.

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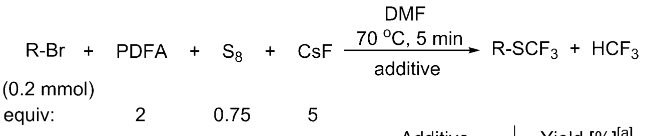
by protonation of CF_3^- anion **A**.[11] However, despite the fact that a decreased yield of SCF_3 products was noted, addition of water did not change the amount of trifluoromethane generated during the reaction (Scheme 2). These observations questioned our initially proposed mechanism and prompted us to conduct further investigations on the mode of formation of the trifluoromethylthio anion **B** from difluorocarbene—a process which was believed to occur by generation of a trifluoromethyl anion.[12]

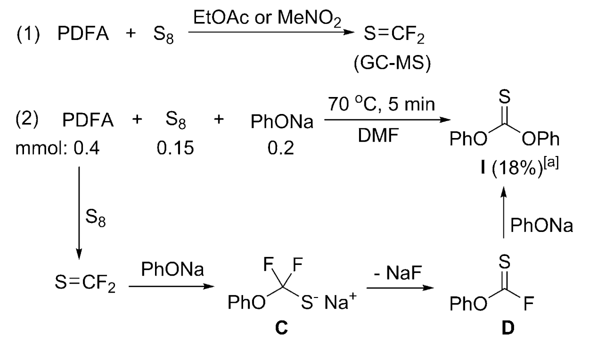


Additive	Yield [%][a]	
none	>99	2
H_2O (1 equiv)	30	1

Scheme 2. The effect of water on trifluoromethylthiolation. [a] Yields were determined by ^{19}F NMR spectroscopy; R = 4-$PhC_6H_4CH_2$.

We speculated that difluorocarbene could react with sulfur directly, on the basis of heterocycle carbenes[13] and metal carbenes[14] that can undergo sulfuration with elemental sulfur to form a C=S bond. We found that elemental sulfur alone can significantly speed up the dissociation of PDFA, suggesting difluorocarbene generated from PDFA may initially react with elemental sulfur instead of fluoride ion. Indeed, the reactive intermediate thiocarbonyl fluoride ($S{=}CF_2$) was observed by heating a mixture of PDFA and elemental sulfur, and detected by GC-MS (electron impact) with ethyl acetate (EtOAc) or $MeNO_2$ as the solvent (Scheme 3, Eq. (1); Supporting Information, Section 2). Furthermore, the addition of sodium phenoxide (PhONa) into the PDFA/S_8 system produced isolable *O*,*O*-diphenyl carbonothioate (Scheme 3, compound **I**) via intermediates **C**/**D**, confirming the formation of thiocarbonyl fluoride during the process (Scheme 3, Eq. (2)).

Notably, although difluorocarbene can be trapped by elemental substances (for example I_2 and Cl_2)[15] sulfuration of difluorocarbene with elemental sulfur has never been realized in the past. All reported preparative methods for thiocarbonyl fluoride, an important fluorinated material,[15,16] necessitate the use of hazardous agents (such as thiophosgene or tetrafluoroethylene) and/or harsh reaction conditions (pyrolysis at 500 °C for example).[16] Safety precaution must also be taken during storage and transfer of thiocarbonyl fluoride obtained by previous approaches[16] because of the chemical's toxicity and low boiling point (−54 °C).[16b] In sharp contrast, synthesis of thiocarbonyl fluoride by our method is convenient and attractive because the reactive material is generated in situ and is rapidly converted in one pot under mild conditions.



Scheme 3. The formation of thiocarbonyl fluoride. [a] Yield of isolated product.

DFT calculations at the M06/6-311+G* level also provided insight into the mechanism for sulfuration of difluorocarbene with elemental sulfur (Figure 1). A weak interaction exists between these two species, meaning that complex **In1** may be formed upon generation of difluorocarbene. A low activation barrier energy (34.21 kJ mol^{-1}) is required to weaken one of the S−S(CF_2) bonds and for :CF_2 to approach the sulfur atom further (**TS1**). The redistribution of electron density in **TS1** leads to the formation of a S−CF_2 bond and a charge separation with a partially positive charge and a partially negative charge on the sulfur atoms of the (CF_2)S and (CF_2S)S groups, respectively (**In2**). A bridged structure (**TS2**) is the transition state for the conversion of intermediates **In2** into **In3**. Intermediate **In3** can be considered as a complex between S_7 and thiocarbonyl fluoride. Dissociation of **In3** affords thiocarbonyl fluoride and S_7, which may undergo iterative reactions with difluorocarbene to provide additional thiocarbonyl fluoride. Successful identification of transition state **TS2** allowed us to calculate the overall activation energy (**In1**→**TS2**) as 66.09 kJ mol^{-1}, which is in agreement with the experimental observation that elemental sulfur can apparently accelerate the dissociation of PDFA. The formation of thiocarbonyl fluoride is thermodynamically favored, as revealed by a relatively low free energy (−207.13 kJ mol^{-1}).

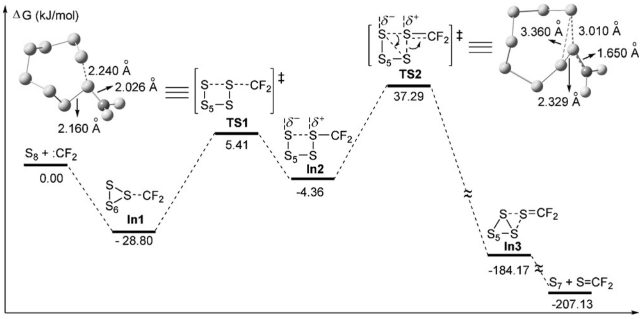
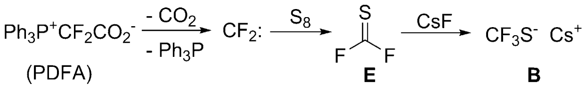


Figure 1. Relative free energies for sulfuration of difluorocarbene calculated at the M06/6-311+G* level.

Based on the mechanistic investigation, it is evident that thiocarbonyl fluoride is a key intermediate for the generation of trifluoromethylthio anion. A revised mechanism is shown in Scheme 4. Decarboxylation of PDFA and the subsequent dissociation of the P−CF_2 bond produce difluorocarbene and triphenylphosphine.[7b] While triphenylphosphine is converted by elemental sulfur into triphenylphosphine sulfide, difluorocarbene readily undergoes sulfuration to give thiocarbonyl fluoride **E**. As a highly electrophilic intermediate,



Scheme 4. The revised mechanism for the formation of trifluoromethylthio anion.

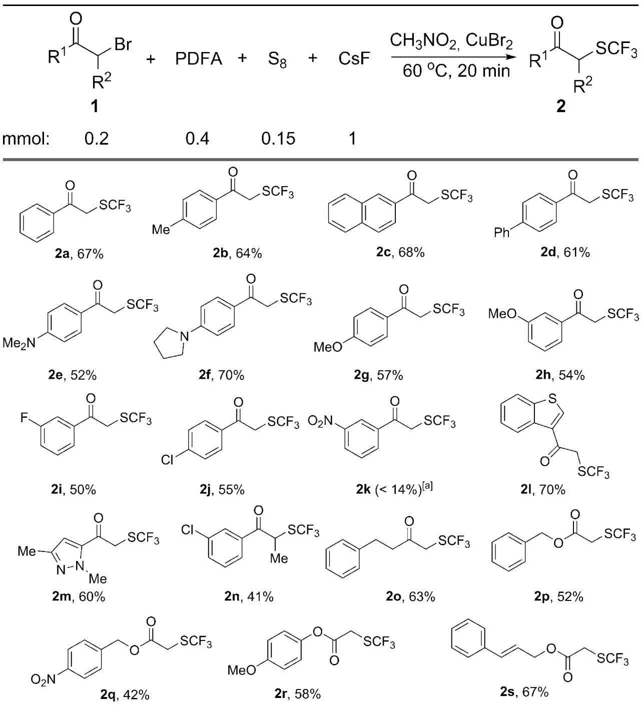
thiocarbonyl fluoride **E** is readily trapped by fluoride to generate trifluoromethylthio anion **B**.

Successful elucidation of the mechanism by which trifluoromethylthio anion is formed allowed us to extend the method to trifluoromethylthiolation of α-bromoketone compounds. However, prior reaction conditions[5] for trifluoromethylthiolation of aliphatic electrophiles were not efficient for the conversion of α-bromoketones, with <1% yield attained in dimethylformamide (DMF) and 2% in nitromethane ($MeNO_2$). To our delight, we found the addition of a copper source substantially increased the yields by 15–20-fold (Supporting Information, Table S1). A quick survey of reaction parameters revealed that efficient transformation of our test substrate, 2-bromoacetophenone with PDFA/S_8/CsF, was achieved in 74% yield by the addition of $CuBr_2$. We have proposed that copper-promoted trifluoromethylthiolation reactions occur by ligand exchange of SCF_3^- with a copper source to generate a [$CuSCF_3$] complex,[17,18] followed by addition and reductive elimination to furnish the final SCF_3 products. Indeed, we have observed the [$CuSCF_3$] complex by ^{19}F NMR spectroscopy in the trifluoromethylthiolation reaction systems (Supporting Information, Section 5), further supporting this proposed reaction pathway.

Under optimized reaction conditions (Supporting Information, Section 3), we investigated substrate scope for trifluoromethylthiolation of α-bromoketones and esters by sulfuration of difluorocarbene (Table 1). The examination of electronic effects on substituents (**2a**–**2k**) in aryl ketones suggested that electron-donating (**2a**–**2h**) and moderately electron-withdrawing (**2i**–**2j**) substituents were favorable for this type of conversion, while a strong electron-withdrawing substituent suppressed the desired reaction (**2k**). The transformation is also compatible with heterocycles (**2l** and **2m**), sterically hindered substrate (**2n**), alkyl ketone (**2o**), and α-bromo esters (**2p**–**2s**).

It is worth mentioning that addition of water into the copper-promoted trifluoromethylthiolation reaction system did not lead to formation of trifluoromethane (Supporting Information). Furthermore, in all these copper-promoted trifluoromethylthiolation reactions, no trifluoromethylated product was observed. Since the substrates are able to undergo copper-promoted trifluoromethylation with trifluoromethyl anion,[9,17] these results (no trifluoromethane and no trifluoromethylation product) further confirmed that trifluoromethyl anion was not the intermediate involved in generation of trifluoromethylthio anion.

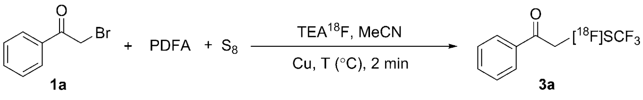
Table 1: The substrate scope for trifluoromethylthiolation of α-bromoketones.



Yields of isolated products. [a] The yield was determined by ^{19}F NMR spectroscopy.

Using α-bromoketone (**1a**) as a model compound, [^{18}F]trifluoromethylthiolation of α-bromoketones was performed and optimized under a comprehensive array of labeling conditions (Supporting Information, Section 6.2). Briefly, azeotropically dried [^{18}F]TEAF (generated in situ from tetraethylammonium bicarbonate (TEAB) and aqueous [^{18}F]fluoride) was used to replace CsF to react with PDFA and S_8, realizing [^{18}F]trifluoromethylthiolation of **1a** with 36% radiochemical conversion (RCC) within 2 min (Table 2, entry 1). Consistent with non-radioactive trifluoromethylthiolation of α-bromo carbonyl compounds, addition of copper catalyst could significantly increase RCC to 64% (Table 2, entry 2). Solvent screening revealed that acetonitrile (MeCN; 72%) provided superior results compared to dimethyl sulfoxide (DMSO; 32%) and DMF (23%; Supporting Information, Table S2). Finally, we found that optimal results were achieved when the reaction was carried out using PDFA (30 μmol) and S_8 (90 μmol) at 40°C, which produced ^{18}F-labeled **3a** in 72% RCC (Table 2, entry 5). Additionally,

Table 2: Radiofluorination conditions.[a]



Entry	PDFA [μmol]	S_8 [μmol]	Copper	*T* [°C]	Yield [%][b]
1	20	60	none	70	36±6
2	20	60	CuI	70	64±6
3	20	60	CuI	40	65±6
4	20	60	CuI	RT	3±2
5	30	90	CuI	40	72±6
6[c]	30	90	CuI	40	8±4

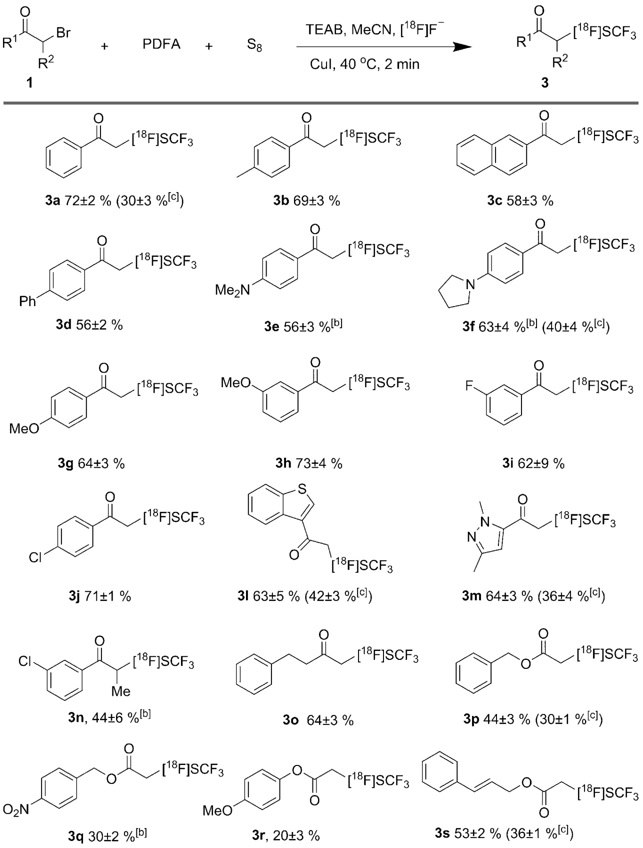
[a] Reaction conditions: precursor (10 μmol), PDFA, S_8, and CuI (10 μmol) in MeCN (400 μL). [b] Radiochemical conversion yields and product identity were determined by radioTLC and radioHPLC, respectively; *n* = 3. [c] Water (1%) was added to the reaction.

[^{18}F]trifluoromethylthiolation showed little tolerance of aqueous conditions with only 8% RCC (Table 2, entry 6).

Reactions with α-bromoketones bearing a phenyl ring with either electron-withdrawing or -donating groups occurred smoothly to afford the corresponding products (Table 3, **3a**–**3j**) >) in 56–73% RCCs. The results of [^{18}F]trifluoromethylthiolation of benzothiophene **3l** (63%) and pyrazole α-bromoketone **3m** (64%) demonstrated the compatibility of this method with heterocyclic substituents. The scope of this method was also extended to aliphatic α-bromoketone **3o** (64%), α-bromo esters **3p** (44%), **3q** (30%), **3r** (20%), and allylic α-bromo ester **3s** (53%). As a proof of concept, [^{18}F]trifluoromethylthiolation products (**3a**, **3f**, **3l**, **3m**, **3p**, and **3s**) were isolated and purified in 30–42% radiochemical yields by semi-preparative HPLC. The specific activity of [^{18}F]**3a** was determined to be 2.02 mCi μmol^{-1} at the end of synthesis (Supporting Information, Section 6.4), which is comparable with reported aryl [^{18}F]-CF$_3$[4g] and aryl-/alkyl-[^{18}F]SCF$_3$ labeling.[5,6]

In summary, our putative understanding of SCF$_3$ formation from difluorocarbene, sulfur, and fluoride ion has been challenged and revised to an unprecedented pathway. Supported by experimental and theoretical studies, we have discovered a new mechanism that operates by sulfuration of difluorocarbene with elemental sulfur. This process is the most convenient synthetic approach to produce thiocarbonyl fluoride, which is an important fluorinated material previously prepared by hazardous agents and/or harsh conditions. This sulfuration method has been developed into a versatile synthetic tool to realize transition-metal-based trifluoromethylthiolation and [^{18}F]trifluoromethylthiolation of α-bromo carbonyl compounds. We envisage that this operationally simple and highly efficient method for generation and transformation of thiocarbonyl fluoride will advance multifluorination research.

Table 3: [^{18}F]Trifluoromethylthiolation of α-bromo carbonyl precursors.[a]



3a 72±2 % (30±3 %[c])
3b 69±3 %
3c 58±3 %
3d 56±2 %
3e 56±3 %[b]
3f 63±4 %[b] (40±4 %[c])
3g 64±3 %
3h 73±4 %
3i 62±9 %
3j 71±1 %
3l 63±5 % (42±3 %[c])
3m 64±3 % (36±4 %[c])
3n, 44±6 %[b]
3o 64±3 %
3p 44±3 % (30±1 %[c])
3q 30±2 %[b]
3r, 20±3 %
3s 53±2 % (36±1 %[c])

[a] All radiochemical reactions were carried out at least three times. Radiochemical conversions and product identity were determined and confirmed by radioTLC and radioHPLC, respectively. [b] Reaction carried out at 80 °C. [c] Yield of isolated products determined by HPLC.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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