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An unconventional mechanistic insight on SCF_3 formation from difluorocarbene and application to ^{18}F -labeled $\alpha\text{-SCF}_3$ carbonyl compounds

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Abstract

We discovered trifluoromethylthiolation occurred through sulfuration of difluorocarbene with elemental sulfur for the first time, which overrides our putative and long-standing trifluoromethyl anion-based theory. This mechanistic elucidation not only allows the discovery of an unprecedented chemical process for the formation of thiocarbonyl fluoride, but also enables transition metal-mediated trifluoromethylthiolation and [^{18}F]trifluoromethylthiolation of α -bromo carbonyl compounds with broad substrate scope and compatibility.

TOC image

The mechanistic investigation reveals that trifluoromethylthio anion from $\text{S}_8/\text{CF}_2/\text{F}^-$ system is generated via sulfuration of difluorocarbene instead of the capture of difluorocarbene by fluoride. This process is well translated to the rapid trifluoromethylthiolation and [^{18}F]trifluoromethylthiolation of α -bromo carbonyl compounds.

Keywords

Difluorocarbene; fluorine; ^{18}F labeling; trifluoromethylthiolation; sulfuration

Over the past several decades, there has been significant advances in the chemistry of difluorocarbene since it has proved to be a valuable and versatile intermediate for organic synthesis, particularly for fluorine incorporation.^[1] As a singlet carbene^[2] and the most stable dihalocarbene,^[1d] difluorocarbene shows moderate electrophilicity due to both strong inductive effect and electron-donating resonance effect induced by fluorine. The understanding of its reactivity has led to 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 protocol,^[5] which is one of the first examples^[5–6] for [^{18}F]trifluoromethylthiolation despite the fact that significant accomplishments have been made for non-radioactive trifluoromethylthiolation. While we have demonstrated the novelty and utility of difluorocarbene in the ^{18}F -trifluoromethylthiolation, the characteristics of these

radiofluorination reactions, including the underlying mechanism and interaction with transition metals, remain elusive and represent a major roadblock to further advance these reactions into the radiolabeling of SCF₃-containing pharmaceuticals, such as Cefazaflur.

Herein we report an unprecedented mechanistic observation of trifluoromethylthio formation among difluorocarbene, sulfur and fluoride, and the subsequent interactions between ensuing SCF₃ 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 leads us to discover a new class of trifluoromethylthiolation for α -bromo carbonyl compounds in the presence of copper complex. As proof of concept, we demonstrate a general and practical copper-mediated radiosynthesis of ¹⁸F-labeled SCF₃ carbonyl compounds with broad substrate scope and functional group compatibility, which is otherwise hardly achievable from traditional methods.

Difluoromethylene phosphobetaine Ph₃P⁺CF₂CO₂⁻ (PDFA), first developed by us^[4i, 4j, 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** in order to obtain final SCF₃ products (Scheme 1).^[5]

However, our 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=CF₂) instead of being trapped by fluoride to give CF₃⁻ 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 by protonation of CF₃⁻ anion **A**.^[11] However, despite the fact that decreased yield of SCF₃ products was noted, addition of water didn't 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 how trifluoromethylthio anion **B** is formed from difluorocarbene, a process which was believed to occur undoubtedly via the generation of trifluoromethyl anion.^[12]

On the basis of heterocycle carbenes^[13] and metal carbenes^[14] that can undergo sulfuration with elemental sulfur to form C=S bond, we speculated that difluorocarbene could react with sulfur directly. 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=CF₂) was observed by heating mixture of PDFA and elemental sulfur and detected by GC-MS (EI) with the use of EtOAc or MeNO₂ as the solvent (Scheme 3, eq 1 and also see supporting information (SI), section 2). Furthermore, the addition of PhONa into the PDFA/S₈ 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).

It is worthy of note that 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 preparation methods for thiocarbonyl fluoride, an important fluorinated material,^[15–16] necessitate the use of hazardous agents, to name a few, thiophosgene or tetrafluoroethylene, and/or harsh reaction conditions, for instance, pyrolysis at 500 °C.^[16] Safety precaution also has to be taken during storage and transfer of thiocarbonyl fluoride obtained by previous approaches^[16] because of its toxicity and low boiling point (–54 °C).^[16b] In sharp contrast, synthesis of thiocarbonyl fluoride from our protocol is convenient and attractive attributed to the efficient method for *in situ* generation and rapid conversion in one pot under mild conditions.

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 the generation of difluorocarbene. A low activation barrier energy (34.21 kJ/mol) is required to weaken one of the S-S(CF₂) bonds and for :CF₂ to approach the sulfur atom further (**TS1**). The redistribution of electron density in **TS1** leads to the formation of S-CF₂ bond and a charge separation with a partially-positive charge and a partially-negative charge on the (CF₂)S and (CF₂S)S atoms, 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 S₇ and thiocarbonyl fluoride. Dissociation of **In3** affords thiocarbonyl fluoride and S₇, which may undergo iterative reactions with difluorocarbene to provide additional thiocarbonyl fluoride. Successful identification of transition state **TS2** allows us to calculate overall activation energy (**In1**→**TS2**) as 66.09 kJ/mol, 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 evidenced by the relatively low free energy (–207.13 kJ/mol).

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 P-CF₂ 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, thiocarbonyl fluoride **E** is readily trapped by fluoride to generate trifluoromethylthio anion **B**.

The successful mechanistic elucidation for the formation of trifluoromethylthio anion enables us to further expand synthetic utility and carry out trifluoromethylthiolation of α-bromo ketone compounds. However, prior reaction conditions^[5] for trifluoromethylthiolation of aliphatic electrophiles were not efficient for the conversion of α-bromo ketones with < 1% yield in DMF and 2% in CH₃NO₂. To our delight, we found the addition of copper source could substantially increase the yields by 15–20 fold (SI, Table

S1). A quick survey of reaction parameters finally revealed that an efficient transformation of our testing substrate, 2-bromoacetophenone with PDFA/S₈/CsF system was achieved in 74% yield by the addition of CuBr₂. We proposed that Cu-promoted trifluoromethylthiolation reactions occurred via ligand exchange of SCF₃[−] with copper source to generate [CuSCF₃] complex,^[17,18] followed by addition-reductive elimination to furnish final SCF₃ products. Indeed, we have observed [CuSCF₃] complex by ¹⁹F NMR spectrometry in the trifluoromethylthiolation reaction systems (SI, section 5), further supporting this proposed reaction pathway.

Under optimized reaction conditions (SI, section 3), we investigated substrate scope for trifluoromethylthiolation of α-bromo ketones and esters via sulfuration of difluorocarbene (Scheme 5). 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 conversions, while strong electron-withdrawing substituent suppressed the desired reaction (**2k**). The transformation is also compatible with heterocycles (**2l–2m**), sterically hindered substrate (**2n**), alkyl ketone (**2o**) and α-bromo esters (**2p–2s**).

It is worth mentioning that addition of water into Cu-promoted trifluoromethylthiolation reaction system did not lead to apparent formation of trifluoromethane (See SI). Furthermore, in all these Cu-promoted trifluoromethylthiolation reactions, no trifluoromethylated product was observed. Since the substrates have proved to be able to undergo Cu-promoted trifluoromethylation with trifluoromethyl anion,^[9, 17] these results (no trifluoromethane and no trifluoromethylation product) further confirmed that trifluoromethyl anion was not the intermediate for the generation of trifluoromethylthio anion.

Using α-bromo ketone (**1a**) as a model compound, [¹⁸F]trifluoromethylthiolation of α-bromo ketones was performed and optimized under a comprehensive array of labeling conditions (SI, section 6.2). Briefly, azeotropically-dried [¹⁸F]TEAF (generated *in situ* from tetraethylammonium bicarbonate (TEAB) and aqueous [¹⁸F]fluoride) was used to replace C₅F to react with PDFA and S₈ to realize [¹⁸F]trifluoromethylthiolation of **1a** in 36% radiochemical conversion (RCC) within 2 min (Table 1, entry 1). Consistent with non-radioactive trifluoromethylthiolation of α-bromo carbonyl compounds, addition of copper catalyst could significantly increase RCC to 64% (entry 2). Solvent screening revealed MeCN (72%) provided superior results than DMSO (32%) and DMF (23%, SI, Table S2). Finally, we found that optimal results were achieved when the reaction was carried out using PDFA (30 μmol) and S₈ (90 μmol) at 40 °C, which produced ¹⁸F-labeled **2a** in 65% RCC (entry 5). In addition, [¹⁸F]trifluoromethylthiolation showed little tolerance of aqueous conditions with only 8% RCC (entry 6).

Reactions with α-bromo ketones bearing both electron-withdrawing and -donating groups on phenyl ring occurred smoothly to afford the corresponding products (Table 2, **3a–3j**) in 56–73% RCCs. The results of [¹⁸F]trifluoromethylthiolation of benzothiophene **3l** (63%) and pyrazole α-bromo ketone **3m** (64%) demonstrated the compatibility of this method to heterocyclic substituents. The scope of this method was also extended to aliphatic α-bromo ketone **3o** (64%), α-bromo ketone esters **3p** (44%) and **3q** (30%), and allylic α-bromo

ketone **3s** (53%). As 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 at the end of synthesis (SI, section 6.4), which is comparable with reported aryl [^{18}F]- CF_3 ^[4g] and aryl-/alkyl- ^{18}F SCF₃ labeling.^[5–6]

In summary, our putative understanding of SCF₃ 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 via sulfuration of difluorocarbene with element sulfur for the first time. This process represents the most convenient synthetic approach to produce thiocarbonyl fluoride, 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 envision this operationally-simple and highly-efficient generation and transformation of thiocarbonyl fluoride will further advance its ability in other multifluorination research areas.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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

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Scheme 2.

The effect of water on trifluoromethylthiolation. ^[a]The yields were determined by ¹⁹F NMR; R = 4-PhC₆H₄CH₂

Scheme 3.

The formation of thiocarbonyl fluoride. ^[a]Isolated yield.

Scheme 4.

The revised mechanism for the formation of trifluoromethylthio anion.

Table 1

Radiofluorination conditions^[a]

Entry	PDFA (μmol)	S ₈ (μmol)	Cu	T (°C)	Yield (%) ^[b] (n = 3)
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: 10 μmol precursor, PDFA, S₈ and 10 μmol CuI in 400 μL MeCN;^[b]radiochemical conversion yields and product identity were determined by radioTLC and radioHPLC, respectively;^[c]1% Water was added in the reaction

Table 2

[¹⁸F]Trifluoromethylthiolation of α-bromo carbonyl precursors^[a]

[a] All radiochemical reactions were carried out at least 3 times. Radiochemical conversions and product identity were determined and confirmed by radioTLC and radioHPLC, respectively.

[b] Reaction was carried out at 80 °C.

[c] Isolated yield by HPLC.