Chinese Chemical Letters 30 (2019) 714–716

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Communication

# $Ph_3P^+CF_2CO_2^-$ as an $F^-$ and $:CF_2$ source for trifluoromethylthiolation of alkyl halides

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ARTICLE INFO

*Article history:*
Received 9 October 2018
Received in revised form 27 October 2018
Accepted 12 November 2018
Available online 13 November 2018

*Keywords:*
Difluorocarbene
Trifluoromethylthiolation
Alkyl halides
Thiocarbonyl fluoride
Fluorine

ABSTRACT

As trifluoromethylthiolation has received increasing attention recently, many $CF_3S$-reagents and trifluoromethylthiolation methods have been developed. Herein we describe trifluoromethylthiolation of alkyl halides by using $Ph_3P^+CF_2CO_2^-$ as a fluoride and difluorocarbene source. Difluorocarbene is a versatile intermediate, but its side reactions are usually ignored and the by-products would therefore be discarded. In this work, a side reaction of difluorocarbene, the generation of a fluoride anion from difluorocarbene, was developed into a synthetic tool. Although the trifluoromethylthiolation reaction involved multi-sequential steps, the cleavage of C–F bond, the formation of $CF_2$=S bond, F-C(S)$F_2$ bond, and C-$SCF_3$ bond, the conversion proceeded fast and was completed within 10 min.


Due to its strong electron-withdrawing effects (Hammett constants $\sigma_p = 0.50$, $\sigma_m = 0.40$) and high lipophilicity (Hansch parameter $\pi = 1.44$) [1–3], trifluoromethylthio group ($CF_3S$) has been of increasing importance in drug design and development. $CF_3S$-containing pharmaceuticals such as Tiflorex, Cefazaflur and Toltrazuril have been continuously developed [4]. Therefore, significant efforts have been directed towards the development of efficient methods for the incorporation of a $CF_3S$ group into organic molecules [4–14]. Compared with traditional methods such as halogen-fluorine exchange [15,16] and trifluoromethylation of sulfur compounds [17,18], direct trifluoromethylthiolation is obviously an efficient and straightforward strategy for $CF_3S$ incorporation [4]. A variety of direct trifluoromethylthiolation approaches have been developed, including electrophilic, radical and nucleophilic trifluoromethylthiolation (Scheme 1, reaction (1)) [19–25]. In these approaches, the synthesis of $CF_3S$-containing reagents is usually required, and the reagents may be expensive, sensitive to air or difficult to prepare. Interestingly, the classic trifluoromethylation reagent, $TMSCF_3$, could also enable the trifluoromethylthiolation in the presence of a sulfur source (reaction (1)) [26–28]. But the trifluoromethylation reagent is quite volatile. Apparently, the development of effective trifluoromethylthiolation protocols by using easily handled reagents is highly desirable.

As a versatile intermediate, difluorocarbene has found widespread application in a wide range of reactions, such as [2 + 1] cyclization and X-H insertion (X = N, O, S, *etc.*) [29,30]. Difluorocarbene is quite electrophilic and thus would be readily trapped by surrounding nucleophiles to generate unavoidable by-products. The side reactions are usually ignored and the by-products would therefore be discarded. However, the development of these unwanted processes into synthetic tools may provide a foundation for the exploration of difluorocarbene chemistry.

$Ph_3P^+CF_2CO_2^-$ (PDFA), a reagent which was developed by our group [31–40] and was also used by other groups [41–46], could be easily prepared *via* a reaction of $Ph_3P$ with $BrCF_2CO_2K$. Pure product could be obtained simply by washing, and the reagent is bench-stable and easy to handle. We have previously found that PDFA could act as an efficient difluorocarbene reagent to realize trifluoromethylthiolation (Scheme 1, reaction (2)) [36,38]. Since an external fluoride anion was used to install the $CF_3S$ moiety and the trifluoromethylthiolation reaction occurred very rapidly (5 min or 20 min), $^{18}F$-trifluoromethylthiolation was examined and successfully achieved [36,38]. Based on our previous observation that side reaction of difluorocarbene would produce a fluoride anion [34],

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https://doi.org/10.1016/j.cclet.2018.11.013
1001-8417/

Previous work:

R-X $\xrightarrow[\text{or } S_8 / [CF_3] \text{ reagent}]{[CF_3S] \text{ reagent}}$ R-SCF$_3$ (1)

R-X $\xrightarrow[\text{with external } F^-]{:CF_2,\ S_8}$ R-SCF$_3$ (2)

X = Cl, Br, *etc.*

This work:

R-X $\xrightarrow[\text{without external } F^-]{:CF_2,\ S_8,\ Cs_2CO_3}$ RSCF$_3$ (3)

X = Cl, Br

**Scheme 1.** Trifluoromethylthiolation strategies.

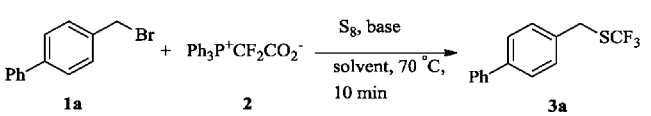
we have now investigated trifluoromethylthiolation by using this difluorocarbene reagent without the presence of an external fluoride anion (Scheme 1, reaction (3)). The generation of fluoride anion from difluorocarbene, a process which has always been considered as a side reaction, was an important chemical step in this protocol. Interestingly, although the trifluoromethylthiolation reaction involved multi-sequential steps, the cleavage of C–F bond, the formation of $CF_2$=S bond, F-C(S)$F_2$ bond, and C-S$CF_3$ bond, the conversion proceeded fast and was completed within 10 min.

As our previous work has shown that DBU [1,8-diazabicyclo [5.4.0]undec-7-ene] could well promote the generation of fluoride anion from difluorocarbene in DMF [34], we then firstly examined the DBU-promoted trifluoromethylthiolation of benzyl bromide (**1a**) with the difluorocarbene reagent $Ph_3P^+CF_2CO_2^-$ in the presence of elemental sulfur ($S_8$) (Table 1, entry 1). The desired product was obtained albeit in a low yield, suggesting that $Ph_3P^+CF_2CO_2^-$ can successfully act as the F- and :$CF_2$ source. A brief survey of the reaction solvents (entries 1–4) revealed that DMA was a superior solvent (entry 2). Besides DBU, various other bases were also screened and some bases were found to be ineffective (entries 5–12). To our delight, 62% yield was obtained by using $Cs_2CO_3$ as a base (entry 12). Increasing the loading of elemental sulfur alone led to a slight decrease in the yield (entries 13 and 14 *vs.* 12). This may be because difluorocarbene would be trapped rapidly by elemental sulfur [38,39] and the generation of fluoride from difluorocarbene would be slightly suppressed. The yield was also decreased by either decreasing or increasing the loading of $Ph_3P^+CF_2CO_2^-$ alone (entries 15 and 16 *vs.* 12). Increasing the loadings of both $Ph_3P^+CF_2CO_2^-$ and $S_8$ increased the yield to 84% (entry 17).

With the optimized reaction conditions in hand (Table 1, entry 17), we then explored the substrate scope of the trifluoromethylthiolation by using $Ph_3P^+CF_2CO_2^-$ as the fluoride and difluorocarbene source (Scheme 2). Electron-rich, -neutral, and –deficient benzyl bromides could all be well converted into the desired products in moderate to good yields (**3a**-**3m**). These conditions could be applied to the conversion of secondary bromides (**3c**). A low isolated yield of **3c** was because of its high volatility (60% $^{19}$F NMR yield was obtained before isolation). Besides benzyl bromides, allyl bromides (**3n**) and alkyl bromides (**3o, 3p**) also showed good reactivity towards this trifluoromethylthiolation. As shown in Scheme 2, a wide range of functional group could be tolerated, such as aryl halides, cyanide, ester, alkene, and heteroarene. Although the electrophilicity of benzyl chlorides is apparently lower than benzyl bromides, trifluoromethylthiolation of benzyl chlorides proceeded smoothly.

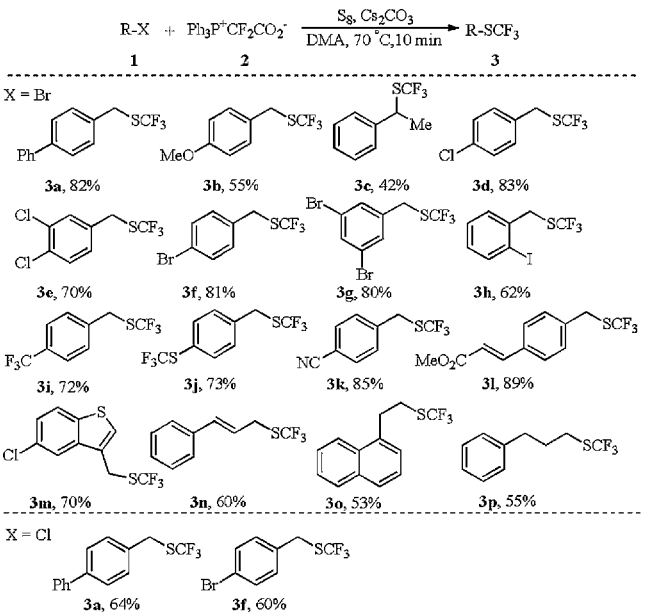
In this trifluoromethylthiolation process, only -$CF_2$- source and S source were present, and thus the question arose as to how the $CF_3S$ moiety was formed in the absence of an external fluoride. It was found that trifluoromethane ($HCF_3$) was rapidly generated as the major product by stirring the mixture of $Ph_3P^+CF_2CO_2^-$ and $Cs_2CO_3$ in DMA (Scheme 3) (details can be found in Supporting information). The low yield (22%) should be because of its low boiling point (−82 °C). No $HCF_3$ was detected by simply heating $Ph_3P^+CF_2CO_2^-$ in DMA without the presence of $Cs_2CO_3$. The observation of $HCF_3$ meant that the reaction of $Ph_3P^+CF_2CO_2^-$ with $Cs_2CO_3$ produced a fluoride anion, which was trapped by difluorocarbene to form $CF_3^-$ anion. Although it has been reported that $CF_3^-$ anion could react with an electrophilic sulfur source to generate $CF_3S^-$ anion [27,47], the formation of $CF_3^-$ anion might not be the predominant path in our reactions. Evidence has been collected in our previous work to reveal that the capture of

**Table 1**
The optimization of the reaction conditions[a].

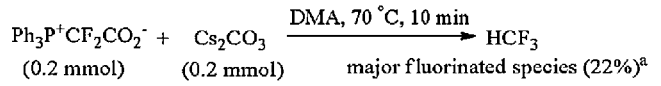



| Entry | Ratio[b] | Solvent | Base | Yield (%)[c] |
|---|---|---|---|---|
| 1 | 1:3:0.75:1 | DMF | DBU | 24 |
| 2 | 1:3:0.75:1 | DMA | DBU | 33 |
| 3 | 1:3:0.75:1 | DME | DBU | 14 |
| 4 | 1:3:0.75:1 | MeCN | DBU | 28 |
| 5 | 1:3:0.75:1 | DMA | $^t$BuONa | ND |
| 6 | 1:3:0.75:1 | DMA | $^t$BuOK | 15 |
| 7 | 1:3:0.75:1 | DMA | $Na_2HPO_4$ | 7 |
| 8 | 1:3:0.75:1 | DMA | $HCO_2Na$ | 18 |
| 9 | 1:3:0.75:1 | DMA | $Na_2CO_3$ | trace |
| 10 | 1:3:0.75:1 | DMA | $Li_2CO_3$ | trace |
| 11 | 1:3:0.75:1 | DMA | $K_2CO_3$ | 52 |
| 12 | 1:3:0.75:1 | DMA | $Cs_2CO_3$ | 62 |
| 13 | 1:3:1:1 | DMA | $Cs_2CO_3$ | 57 |
| 14 | 1:3:1.25:1 | DMA | $Cs_2CO_3$ | 53 |
| 15 | 1:2:0.75:1 | DMA | $Cs_2CO_3$ | 45 |
| 16 | 1:4:0.75:1 | DMA | $Cs_2CO_3$ | 53 |
| 17 | 1:4:1.25:1 | DMA | $Cs_2CO_3$ | 84 |

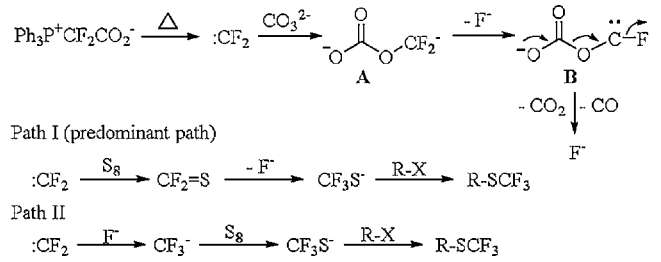
[a] Reaction conditions: substrate **1a** (0.2 mmol), $Ph_3P^+CF_2CO_2^-$, $S_8$, base, and solvent (3 mL) at 70 °C for 10 min; DME = 1,2-dimethoxyethane.
[b] Molar ratio of **1a**:**2**:$S_8$:base.
[c] The yields were determined by $^{19}$F NMR spectroscopy.




**Scheme 2.** Substrate scope of trifluoromethylthiolation. Isolated yields. Reaction conditions: substrate 1 (0.2 mmol), $Ph_3P^+CF_2CO_2^-$ (4 equiv.), $S_8$ (1.25 equiv.), $Cs_2CO_3$ (1 equiv.), and DMA (3 mL) at 70 °C for 10 min.




**Scheme 3.** The evidence for the generation of a fluoride anion from difluorocarbene. [a]The yield was determined by $^{19}F$ NMR spectroscopy.




**Scheme 4.** The proposed mechanism.

difluorocarbene by elemental sulfur to give thiocarbonyl fluoride is a very fast process [38,39]. Besides, as shown in entries 13 and 14 in Table 1, increasing the loading of elemental sulfur alone led to a slight decrease in the yield. This should be because the generation of fluoride anion was suppressed by the more rapid process, the capture of difluorocarbene by elemental sulfur.

On the basis of the above results, we propose the reaction mechanism as shown in Scheme 4. Warming conditions lead to the generation of difluorocarbene from $Ph_3P^+CF_2CO_2^-$ [31–40]. Difluorocarbene is electrophilic and would thus be easily trapped by cesium carbonate to form dianion **A**. $\alpha$-Fluoride elimination of intermediate **A** produces carbene **B**, which collapses to release carbon dioxide and carbon oxide [34], and generates fluoride anion. The rapid capture of difluorocarbene by elemental sulfur provides thiocarbonyl fluoride, which is also quite electrophilic and the attack of fluoride at this species gives trifluoromethylthio anion ($CF_3S^-$) (Path I). Nucleophilic substitution of a substrate with $CF_3S^-$ anion furnishes the final product. Even though the formation of $CF_3^-$ anion and its attack at elemental sulfur to form $CF_3S^-$ anion is not the predominant path (Path II), this process may not be excluded.

In summary, we have described the trifluoromethylthiolation of alkyl halides by using $Ph_3P^+CF_2CO_2^-$ as a fluoride and difluorocarbene source. The development of a side reaction of difluorocarbene, a process which is usually ignored in organic synthesis, into a synthetic tool may provide foundation for the exploration of difluorocarbene chemistry. The trifluoromethylthiolation process occurred rapidly even though the reaction involved multi-sequential steps, the cleavage of C–F bond, the formation of $CF_2$=S bond, F-C(S)$F_2$ bond, and C-$SCF_3$ bond. As the difluorocarbene reagent, $Ph_3P^+CF_2CO_2^-$, could be easily prepared and is easy to handle, this trifluoromethylthiolation protocol may find application in the synthesis of $CF_3S$-containing biologically active molecules.

## Acknowledgments

We thank the National Basic Research Program of China (No. 2015CB931903), the National Natural Science Foundation of China (Nos. 21421002, 21472222, 21502214, 21672242, 81273537), the Chinese Academy of Sciences (Nos. XDA02020105, XDA02020106), the Key Research Program of Frontier Sciences (CAS) (No. QYZDJSSW-SLH049), the Key Project of Hunan Provincial Education Department (No. 17A190), the Zhengxiang Scholar Program of the University of South China, Hunan Provincial Hengyang City Joint Fund (No. 2017JJ4050), Hunan Graduate Science and Technology Innovation Projects (No. 2018-400), Program for Innovative Talent Team of Hengyang (No. 2017-1), the Key Project of Hengyang Science and Technology Department (No. 2017KJ166), and Shanghai Research Institute of Chemical Industry Co., LTD. (No. SKL-LCTP-201802) for financial support.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2018.11.013.

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