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Communication

Synthesis of *S*-monofluoromethyl phosphorothioates from P^V-H compounds and $PhSO_2SCH_2F$

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ABSTRACT

S-Monofluoromethyl phosphorothioates represent an important class of organofluorine compounds and are reported here for the first time. A series of *S*-monofluoromethyl phosphorothioates are conveniently synthesized from different P^V-H compounds and $PhSO_2SCH_2F$ under mild conditions. The method is compatible with common functional groups and provides potential opportunities to synthesize new bioactive molecules for medicinal chemistry.

In the last few decades, fluorine-containing compounds have received considerable interest in the fields of life science and materials science due to unique "fluorine effect" [1–7]. The introduction of the fluorine atom or fluorinated group into the specific position of the molecules has been a powerful method to tune the properties of the functional molecules [8–16]. Recently, fluoroalkylthio groups, such as trifluoromethylthio (-SCF_3) [17–23], difluoromethylthio (-SCF_2H) [24–31], monofluoromethylthio (-SCH_2F) [32,33] have drawn more attention from medicinal chemists owing to their high lipophilicity and metabolic stability. Various reagents and methods have been developed to prepare fluoroalkylthiolated compounds [34,35]. Compared to the extensive reports on trifluoromethylthio (-SCF_3) and difluoromethylthio (-SCF_2H) compounds, the studies on the monofluoromethylthio (-SCH_2F) compounds are very limited because of the lack of efficient monofluoromethylthiolating reagents and methods. The known monofluoromethylthio compounds have demonstrated their huge potential in pharmaceutical industry, evidenced by the anti-inflammatory drug fluticasone propionate [36] and nonsteroidal antiflammatory agent cathepsin K inhibitors [37] (Fig. 1a). Therefore, it is an urgent task to prepare diverse monofluoromethylthio compounds to meet increasing demand for medicinal chemistry.

However, to date, the reports on monofluoromethylthio compounds are mainly limited to monofluoromethyl thioethers [38] and monofluoromethyl carbothioates (Figs. 1b and c). To the best of our knowledge, *S*-monofluoromethyl phosphorothioates are not reported yet, even they represent an important class of monofluoromethylthio compounds. Phosphorothioates have been used to substitute the native phosphate backbones to increase metabolic stability and cellular uptake in antisense oligonucleotide therapeutics [39,40]. Thus, the *S*-fluoroalkylphosphorothioates might provide new opportunities for the development of new bioactive molecules in virtue of the advantage of fluorine. Actually, *S*-fluoroalkyl phosphorothioates were scarce and only *S*-trifluoromethyl phosphorothioates were reported in the literatures [41–43]. However, the *S*-trifluoromethyl phosphorothioates were thermally labile and prone to lose SCF_2 to generate fluorophosphates, which limited their practical applications. Herein, we report a simple and efficient method to synthesize *S*-monofluoromethyl phosphorothioates from P^V-H compounds and $PhSO_2SCH_2F$ under mild conditions (Fig. 1d).

We firstly chose commercially available diphenylphosphine oxide and monofluoromethylthiolating reagent ($PhSO_2SCH_2F$) **1**, which was developed by Shen and Lu [44], as the model substrates to optimize the reaction conditions (Table 1). The initial reaction condition was set at room temperature for 4 h. To our delight, the reaction occurred smoothly in 1,2-dichloroethane without additives and afforded the corresponding monofluoromethylthiolated

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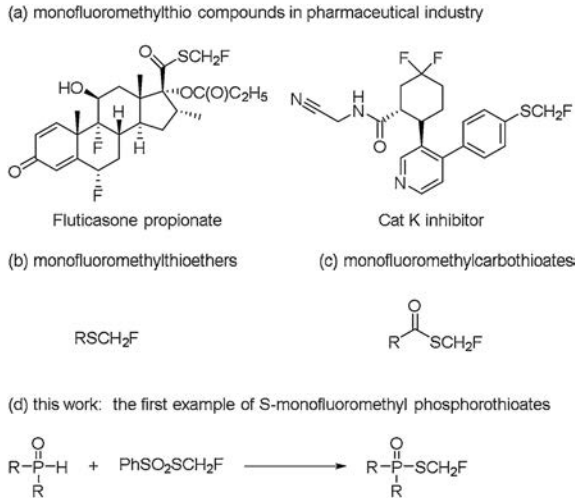
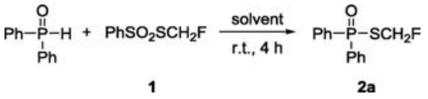


Fig. 1. The approach for the preparation of S-monofluoromethyl phosphorothioates.

Table 1
Optimization of the reaction conditions for diphenylphosphineoxide.[a]



Entry	Reagent **1** (equiv.)	Solvent	Yield (%)[b]
1	1	DCE	79
2	1.5	DCE	86
3	1.5	EA	94
4	1.5	CH_2Cl_2	92
5	1.5	$CHCl_3$	90
6	1.5	DEE	90
7	1.5	THF	90
8	1.5	1,4-dioxane	59
9	1.5	DMF	74
10	1.5	DMSO	73
11	1.5	MeOH	54
12	1.5	EtOH	78
13	1.5	CH_3CN	77
14	1.5	acetone	57

DCE = 1,2-dichloroethane. DEE = diethyl ether. EA = ethyl acetate.

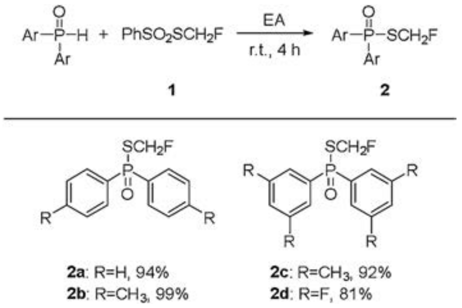
[a] Reaction conditions: diphenylphosphine oxide (0.50 mmol), reagent **1** (0.75 mmol) in solvent (5.0 mL), at room temperature for 4 h under air.

[b] Isolated yields of **2a**.

product **2a** in 79% isolated yield (Table 1, entry 1). When the amount of $PhSO_2CH_2F$ was increased to 1.5 equiv., the reaction gave full conversion of diphenylphosphine oxide and the yield of product was increased to 86% (Table 1, entry 2). Further solvent screening showed that the reaction could work in common organic solvents. The reaction in ethylacetate afforded the desired product in highest 94% yield (Table 1, entry 3). Other solvents such as dichloromethane, chloroform, diethyl ether, tetrahydrofuran were also very effective for this reaction, while more polar solvents such as 1,4-dioxane, DMF, DMSO, CH_3OH, C_2H_5OH, CH_3CN and acetone gave the product in lower yield (Table 1, entries 4–14). With the optimal conditions in hand, we expanded the scope of substrates. As shown in Scheme 1, both electron-rich and electron-deficient diphenylphosphine oxides reacted smoothly to afford the corresponding products in good yields (**2a**-**2d**).

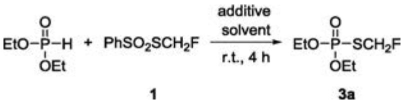
Subsequently, we turned our attention to the reaction of the *H*-phosphonate with reagent **1** to prepare diverse *S*-monofluoro-methyl phosphorothioates. Surprisingly, under the same conditions, the reaction of diethyl phosphonate with reagent **1** was sluggish and only gave the product **3a** in 4% yield (Table 2, entry 1). With the addition of triethylamine, this reaction was significantly promoted and afforded the product in 59% yield (Table 2, entry 2). The yield was increased to 88% when 1.0 equiv. of triethylamine was added (Table 2, entry 3) and the excess of triethylamine did not help to improve the yield (Table 2, entry 4). The solvents and reaction time were also quickly screened and it was found that the reaction in diethyl ether gave the highest 95% yield (Table 2, entry 6), whereas the longer reaction time will decrease the yield (Table 2, entries 7 and 8).

Based on the optimized conditions in entry 6 of Table 2, we next investigated the substrate scope of this protocol (Scheme 2). In general, dialkyl/monoalkyl/diaryl *H*-phosphonates were applicable and gave the products in moderate and excellent yields. Specifically, hindered *H*-phosphonate such as diisopropyl phosphonate, diisobutyl phosphonate and dibenzyl phosphonate also reacted smoothly to give the products in 86%, 95% and 93% yield, respectively (**3c**, **3e** and **3h**). Nevertheless, more hindered ditertbutyl phosphonate did not react with reagent **1** under the standard condition. Furthermore, diarylphosphonate, for example, diphenylphosphonate also reacted to produce the corresponding *O*,*O*-diphenyl *S*-monofluoromethyl phosphorothioates product in 74% yield (**3g**). In addition, the reaction of monoalkyl phenyphosphonates with reagent **1** gave the full conversion within 1h and afforded the desired product in good yields (**3m**-**3o**), which is



Scheme 1. Scope of monofluoromethylthiolation of diarylphosphine oxides. Reaction conditions: diaryphosphine oxides (0.50 mmol), reagent **1** (0.75 mmol) in ethyl acetate (5.0 mL), at room temperature for 4 h, under air. All yields given are isolated yields.

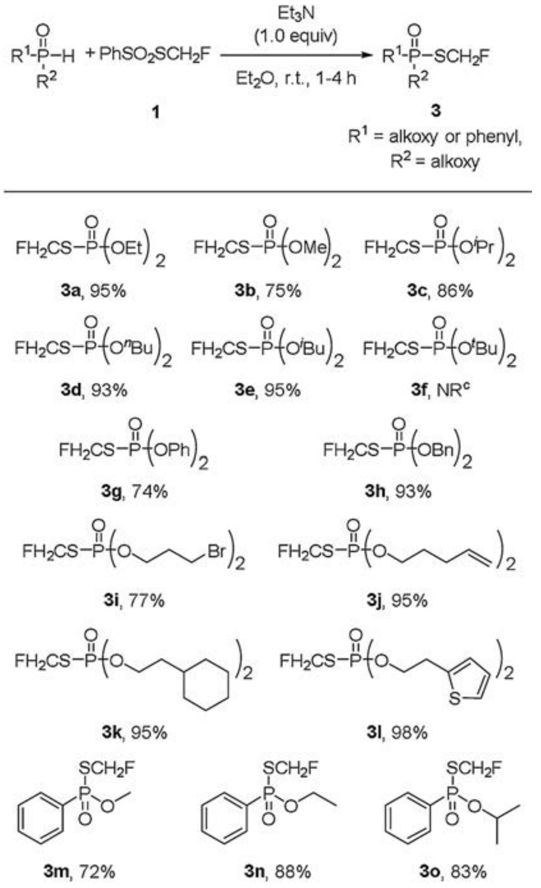
Table 2
Optimization of the reaction conditions for diethyl phosphonate.[a]



Entry	Additive (equiv.)	Solvent	Time (h)	Yield (%)[b]
1	–	EA	4	4
2	Et_3N (0.5)	EA	4	59
3	Et_3N (1.0)	EA	4	88
4	Et_3N (1.5)	EA	4	86
5	Et_3N (1.0)	CH_2Cl_2	4	90
6	Et_3N (1.0)	DEE	4	95
7	Et_3N (1.0)	DEE	6	75
8	Et_3N (1.0)	DEE	8	60

[a] Reaction conditions: diethyl phosphonate (0.5 mmol), **1** (0.75 mmol) and Et_3N (0.5 mmol) in solvent (5.0 mL), at room temperature for 4 h under air.

[b] Isolated yields of **3a**.

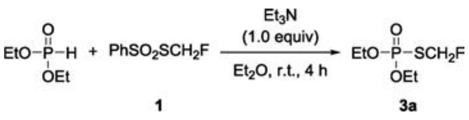


Scheme 2. Scope of monofluoromethylthiolation of *H*-phosphonate. *H*-Phosphonate (0.5 mmol), **1** (0.75 mmol) and Et_3N (0.5 mmol) in diethyl ether (5.0 mL), at room temperature for 1-4 h, under air. All yields given are isolated yields.

faster than that of dialkyl phosphonates. Due to mild conditions, the common functional groups such as, bromide (**3i**), alkenyl (**3j**), cycloalkyl (**3k**) and thienyl (**3l**) were well-tolerated in this reaction.

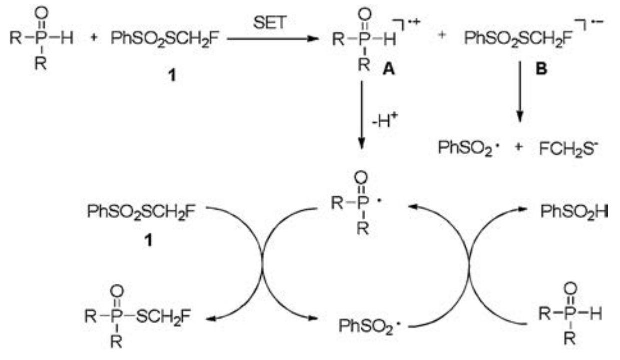
Reagent **1** was previously reported as a radical ($\cdot SCH_2F$) precursor in the monofluoromethylthiolation reaction of aldehyde [45] and the addition reaction of unactivated alkene with reagent **1** [44]. To further explore the reaction mechanism whether this reaction involved the radical pathway, we conducted a series of controlled experiments. Two free radical trapping agents, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and dibutylhydroxy-toluene (BHT) were added to the standard reaction of $PhSO_2SCH_2F$ with diethyl phosphonate. It was found that the two reactions were largely retarded and gave the product in 13% and 12% yield respectively, suggesting that the radical wasinvolved in the transformation (Table 3, entries 2 and 3). Furthermore,thereactionof $PhSO_2SCH_2F$ with diethyl phosphonate was partially inhibited by the addition of 1.0 equiv. of a single-electron-transfer (SET) inhibitor 1,4-dinitrobenzene and 1,3-dinitrobenzene under standard conditions (Table 3, entries 4 and 5). Since this reaction occurred without the addition of the radical initiator, a single electron transfer process might be involved, where diethyl phosphonate itself acted as electron donor and initiated this reaction.

Table 3
Control experiments of reagent **1** with diethyl phosphonate.[a]



Entry	Change of standard conditions	Yield (%)[b]
1	–	95
2	TEMPO (1.0 equiv.)	13
3	BHT (1.0 equiv.)	12
4	*p*-dinitrobenzene (1.0 equiv.)	70
5	*m*-dinitrobenzene (1.0 equiv.)	65

[a] Reaction conditions: diethyl phosphonate (0.5 mmol), **1** (0.75 mmol) and Et_3N (0.5 mmol) in solvent (5.0 mL), at room temperature for 4 h under air.
[b] Isolated yields of **3a**.



Scheme 3. Plausible mechanism.

Based on these experiments and the related literatures [24,32,45–47], we proposed a tentative mechanism for the reaction of P^V-H compounds with reagent **1** ($PhSO_2SCH_2F$) (Scheme 3). In the reaction, P^V-H compound donated a single electron to $PhSO_2SCH_2F$ to form the radical cation **A** and radical anion **B**. Then the resulting radical cation **A** loses proton to generate phosphoryl radical, meanwhile, anion **B** decomposes to $PhSO_2$ radical and monofluoromethylthiol anion. The phosphoryl radical reacts with $PhSO_2SCH_2F$ to give the corresponding *S*-monofluoromethyl phosphorothioates, together with the formation of $PhSO_2$ radical [44]. The generated $PhSO_2$ radical might abstract the hydrogen of P^V-H compound to produce the phosphoryl radical and $PhSO_2H$ to finish the radical chain cycle. More details about the mechanism of the reaction are ongoing.

In conclusion, *S*-monofluoromethyl phosphorothioates, as an important class of monofluoromethylthio compounds, are reported for the first time. *S*-Monofluoromethyl phosphorothioates were synthesized from monofluoromethylthiolated reagent $PhSO_2SCH_2F$ and different P^V-H compounds including diarylphosphine oxides and *H*-phosphonate. Due to the mild conditions, this reaction is compatible with common function groups. Preliminary mechanistic studies suggest this reaction might proceed *via* a single-electron-transfer pathway. This method provides potential opportunities to synthesize new bioactive molecules for medicinal chemistry.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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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.2020.05.032.

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