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Synthesis of Difluoromethylthioesters from Aldehydes

Shi-Huan Guo, Xing-Long Zhang, Gao-Fei Pan, Xue-Qing Zhu, Ya-Ru Gao, and Yong-Qiang Wang*

Abstract: Difluoromethylthioester compounds as another important kind of organofluorine compounds are reported for the first time. They can be facilely and efficiently synthesized from various aldehydes. The synthetic method is featured by mild reaction conditions, good tolerance of functional groups, broad substrate scope, and especially no metal involving in the reaction. The approach has the potential to become an important tool for the late-stage functionalization of advanced synthetic intermediates, and should have many applications in medical chemistry.

About 25% of pharmaceuticals and 40% of agrochemicals on the market contain fluorine atoms.[1] Accordingly, the incorporation of fluorine atoms into molecules has become standard procedure in the discovery of such new active substances.[2] Recently, difluoromethylthiol (-SCF_2H) group has drawn exceptional attention because its acidic proton as a hydrogen bonding donor[3] could enhance the drug molecule's binding selectivity,[4] and its electron-withdrawing nature could increase the drug molecule's metabolic stability, and its distinctive Hansch parameter (π_R = 0.68)[5] would provide medicinal chemists the opportunity to fine tune the drug molecule's lipophilicity. To date, there are numerous reports on difluoromethylthiolated compounds about their synthesis and bioactivity,[6,7] which should permit the effective design of novel drug candidates.[8] Indeed, several difluoromethylthioethers residues have been demonstrated to be uniquely efficient, such as the *β*-lactamase-resistant oxcephalosporin antibiotic Flomoxef sodium[9] and insecticide Pyriprole[10] (Figure 1a).

However, to the best of our knowledge, the present reports were limited in the difluoromethylthioether compounds (Figure 1b),[6,7] and there is no case of difluoromethylthioester compounds reported (Figure 1c) though they are another important kind of difluoromethylthiol compounds. Due to different chemical property of difluoromethylthioester from that of difluoromethylthioether, difluoromethylthioester compounds would predictably derive new bioactive molecules which have been indirectly demonstrated by anti-inflammatory monofluoromethylthioester drug Fluticasone and its derivative Fluticasone propionate (Figure 1d).[11] Herein, we firstly disclose a facile and efficient synthesis of difluoromethylthioesters from aldehydes and a difluoromethylthiol reagent through an intermolecular radical process (Figure 1e).

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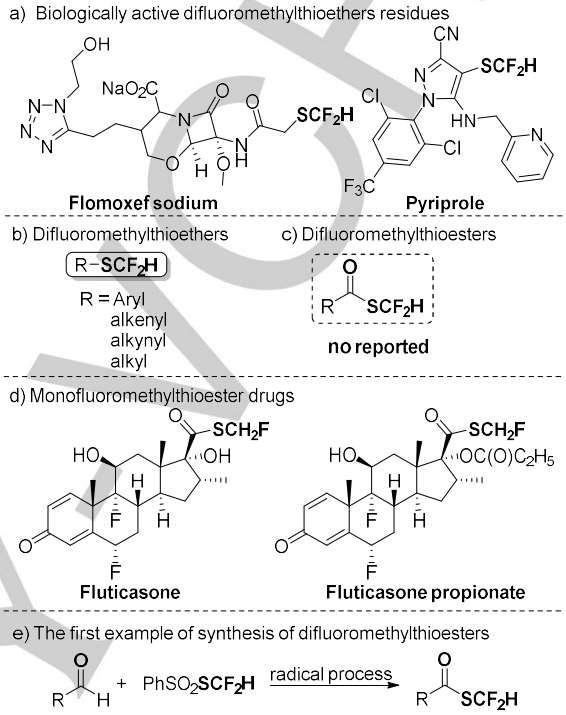

Figure 1. Difluoromethylthiolether, Monofluoromethylthioester Compounds and the First Synthesis of Difluoromethylthioesters from Aldehydes.

Aldehydes are cheap and abundant chemical materials, and they can serve as versatile acyl radical precursors in the reactions.[12a] Therefore, we envisaged if the desired difluoromethylthioesters could be produced by incorporation difluoromethylthiol radical (·SCF_2H) with acyl radicals that come from aldehydes. In order to examine this idea, we initially chose *p*-tolualdehyde (**1a**) as acyl radical precursor, and three difluoromethylthiolation reagents (**2a**, **2b**, and **2c**)[7k,3v] respectively as difluoromethylthiol radical source, employing *di-tert*-butyl peroxide (DTBP) as radical initiator, 1,2-dichloroethane as solvent at reflux temperature (Table 1, entries 1-3). Gratifyingly, the desired difluoromethylthioester **3a** was obtained in 35% yield after 24 h with difluoromethylthiolation reagent **2b** which was developed by Lu and Shen and could be readily prepared from **2a** by two steps (entry 2).[7v] Encouraged by these meaningful results, with **1a** and **2b** as the substrates, other radical initiators, such as *tert*- butyl hydroperoxide (TBHP, 70 wt. % in H_2O), $K_2S_2O_8$, $(NH_4)_2S_2O_8$, and H_2O_2 (30 wt. % in H_2O) were then tested. TBHP (70 wt. % in H_2O) was found to be superior to the others with a slightly higher yield (38%) (entries 4 – 7). The influence of the solvent was next studied (entries 8 – 14). To our delight, CH_3CN afforded corresponding difluoromethylthioester **3a** in 53% isolated yield (entry 11). When the amount of TBHP was increased to 2.0 equiv, the yield was improved to 87% (entry 15). Interestingly, a similar result was obtained when the reaction was performed under an Ar atmosphere (entry 16). The control experiment showed that the

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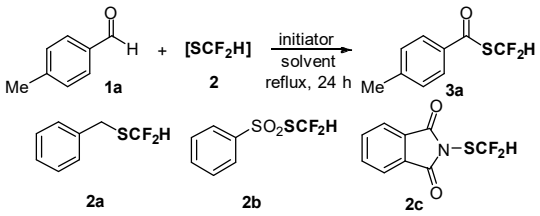
Table 1. Optimization of the Reaction Conditions for Difluoromethylthiolation[a]

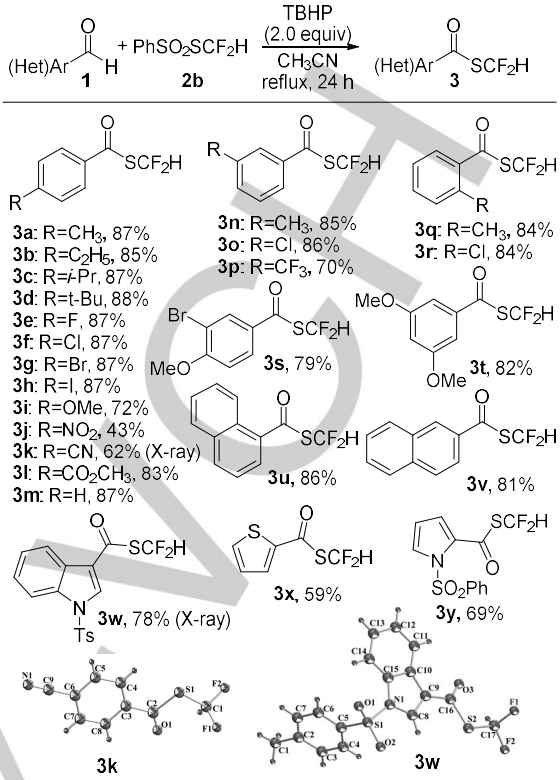


entry	2	initiator (x equiv)	solvent	conv. (%)[b]	yield (%)[c]
1	**2a**	DTBP (1.0)	1,2-dichloroethane	0	-
2	**2b**	DTBP (1.0)	1,2-dichloroethane	43	35
3	**2c**	DTBP (1.0)	1,2-dichloroethane	0	-
4	**2b**	TBHP (1.0)	1,2-dichloroethane	45	38
5	**2b**	$K_2S_2O_8$ (1.0)	1,2-dichloroethane	25	17
6	**2b**	$(NH4)_2S_2O_8$ (1.0)	1,2-dichloroethane	23	15
7	**2b**	H_2O_2 (1.0)	1,2-dichloroethane	15	8
8	**2b**	TBHP (1.0)	$CHCl_3$	31	21
9	**2b**	TBHP (1.0)	DMSO	18	-
10	**2b**	TBHP (1.0)	DMF	15	-
11	**2b**	TBHP (1.0)	CH_3CN	60	53
12	**2b**	TBHP (1.0)	toluene	19	11
13	**2b**	TBHP (1.0)	THF	12	-
14	**2b**	TBHP (1.0)	H_2O	25	17
15	**2b**	TBHP (2.0)	CH_3CN	100	87
16[d]	**2b**	TBHP (2.0)	CH_3CN	100	86
17	**2b**	-	CH_3CN	12	6

[a] Reaction conditions: **1a** (0.75 mmol), **2** (0.5 mmol), initiator, solvent (2.5 mL), at reflux tempreture under air. [b] Based on **2**. [c] Isolated yields of **3a**. [d] Under Ar. DTBP = di-*tert*-butyl peroxide. TBHP = *tert*-butyl hydroperoxide (70 wt. % in H_2O). conv. = conversion.

difluoromethylthioester **3a** was obtained in only 6% yield when the reaction was carried out in the absence of TBHP (entry 17); the small amount of the product might result from thermal-induced radical reaction.[12a,13] Thus, the optimized reaction conditions for the synthesis of difluoromethylthioesters **3a** were identified as the following: **1a** (0.75 mmol), **2b** (0.5 mmol), TBHP (1.0 mmol), and CH_3CN (2.5 mL) at 82 °C.

With optimized reaction conditions in hand, substrate scope of the transformation was investigated (Scheme 1). In general, the reactions of a variety of aryl aldehydes bearing either electron-donating groups or electron-withdrawing groups occurred with moderate to high yields (**3a** – **3t**). A broad range of common functional groups such as alkyls (**3a** – **3d**), halides (F, Cl, Br, I,

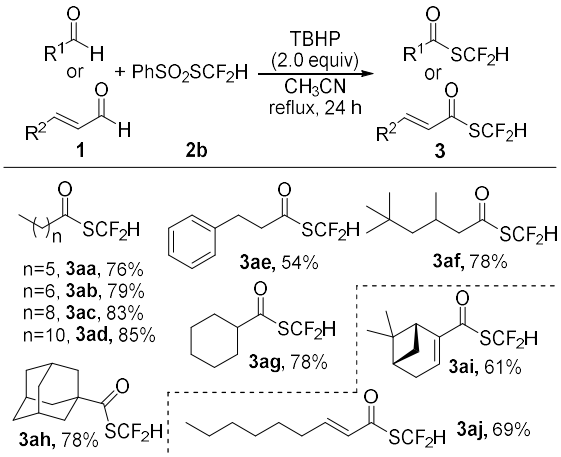


Scheme 1. Scope of Difluoromethylthiolation of (Hetero)aromatic Aldehydes. Reaction conditions: **1** (0.75 mmol), **2b** (0.5 mmol), TBHP (1.0 mmol, 70 wt.% in H_2O), and CH_3CN (2.5 mL) at 82 °C. All yields given are isolated yields.

3e – **3h**), ether (**3i**, **3s**, and **3t**), ester (**3l**), nitro (**3j**), and cyano groups (**3k**) were compatible with this process, which offered valuable synthetic handles for further transformations. Particularly noticeable is the performance of 4-iodobenzaldehyde (**1h**) in the reaction. On the basis of Shen's study,[5c] I also was possible difluoromethylthiolation site, so **1h** contains two possible reaction sites. Surprisingly, it provided difluoromethylthioester **3h** as the sole difluoromethylthiolation product in 87% yield. The position of substitution groups on the phenyl ring has no effect on this reaction (**3a**, **3n**, and **3q**). The reaction with naphthyl aldehydes also proceeded smoothly (**3u** and **3v**). Heteroarenes are prevalent in many biologically relevant molecules. Therefore, aldehydes containing thiophene, indole, and pyrole motifs were subjected to the reaction conditions. Pleasingly, they provided the desired products in good yields (**3w** – **3y**) with no by-products resulting from radical addition to the heterocyclic rings observed. The structure of difluoromethylthioesters **3k** and **3w** were unambiguously confirmed by single-crystal X-ray diffraction analysis.

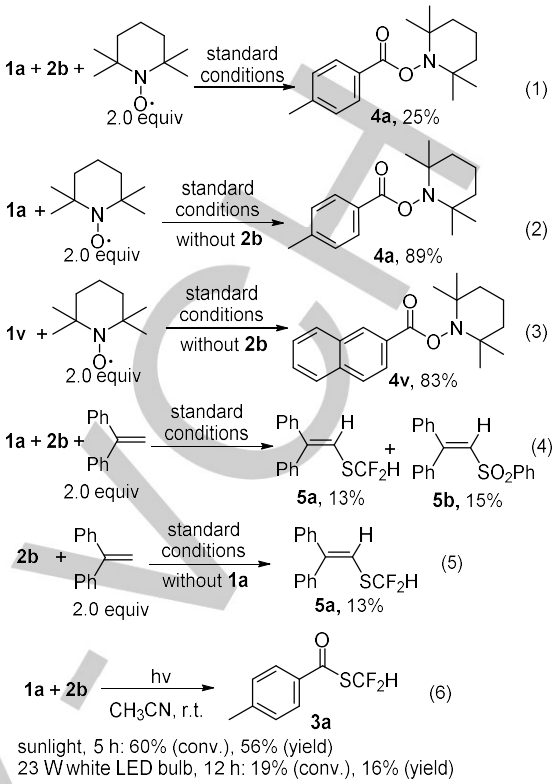
Encouraged by the success of (hetero)aromatic aldehydes, aliphatic aldehydes and *α*, *β*-unsaturated aldehydes were then investigated.[14] As summarized in Scheme 2, the reactions of a variety of aliphatic aldehydes with **2b** proceeded smoothly under above standard conditions to give the corresponding difluoromethylthioesters (**3aa** – **3aj)** in good yields. It is worth mentioning that not only primary aliphatic aldehydes (**1aa** – **1af**) and secondary aliphatic aldehydes (**1ag**) but also tertiary aliphatic aldehydes (**1ah**) were suitable substrates. The efficacy of the methodology was further verified by the compatibility of *α,*

β-unsaturated aldehyde. (-)-Myrtenal (**1ai**) and *(E)*-non-2-enal (**1aj**) could be successfully converted into the corresponding difluoromethylthioesters **3ai** and **3aj** in good yields. All difluoromethylthioesters above are not air and moisture sensitive. No detectable decomposition was observed after more than a month of storage at ambient temperature. Considering some aldehydes are expensive, two experiments of materials ratio were carried out. **1a** and **2b** with the ratio of 1:1 or 1:1.2, both reacted smoothly using TBHP (2.0 equiv) as radical initiator, CH_3CN as solvent at reflux temperature to afford **3a** in 81% and 90% yields, respectively.



Scheme 2. Scope of Difluoromethylthiolation of Aliphatic Aldehydes and *α, β*-Unsaturated Aldehydes. Reaction conditions: **1** (0.75 mmol), **2b** (0.5 mmol), TBHP (1.0 mmol, 70 wt.% in H_2O), and CH_3CN (2.5 mL) at 82 °C. All yields given are isolated yields.

To understand the mechanism of this reaction, we carried out a series of radical-trapping experiments. First, under the standard reaction conditions, TEMPO (2.0 equiv) was introduced into the reaction system of **1a** with **2b**. After 24 h at reflux, 68% of **1a** was recovered while **2b** was completely consumed, and a main product, namely the adduct (**4a**) of **1a** with TEMPO, was isolated in 25% yield [Eq. (1)], indicating acyl radical existed in reaction system. Then two control experiments were implemented under the standard conditions. Without difluoromethylthiol reagent **2b**, aldehydes **1a** and **1v** reacted with TEMPO, affording **4a** and **4v** in 89% and 83% yields, respectively [Eq. (2) and (3)]. The two control experiments further demonstrated that acyl radical was very likely involved in the difluoromethylthiolation reaction. Without aldehyde, **2b** with TEMPO presented mess reaction. Next, under the standard reaction conditions, another classical radical-trapping reagent 1, 1-diphenylethylene was introduced into the reaction system of **1a** with **2b**. After 24 h at reflux, most of **1a** and **2b** were recovered, while adducts **5a** and **5b** were isolated in 13% and 15% yields, respectively [Eq. (4)], showing SCF_2H radical and $PhSO_2$ radical likely existed in reaction system. Without aldehyde **1a**, 1, 1-diphenylethylene reacted with **2b** under above standard conditions also affording **5a** in 13% [Eq. (5), 85% **2b** recovered].[15] Finally, visible light-promoted experiments were investigated. Reactions carried out by irradiation with natural sunlight (5 h) or a commercially available 23 W white LED bulb



(12 h) to give **3a** in 56% and 16% yields, respectively [Eq. (6)]. The photoreactions again supported the radical process of the transformation.

In literature,[7v] **2b** was demonstrated to be an efficient reagent for radical difluoromethylthiolation. Based on these results and the related literatures,[7v,12,16] a tentative reaction mechanism for the synthesis of difluoromethylthioesters was proposed in Figure 2. The reaction begins with abstraction of H from aldehyde (**1**) by TBHP to generate acyl radical **A**. Then acyl radical **A** reacts with **2b** affording desired product (**3**) and $PhSO_2$ radical which has been reported by the literatures[16] and is also supported by product **5b** isolated. Further investigations on more detailed mechanism are ongoing.

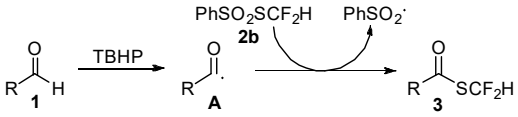


Figure 2. Plausible Mechanism.

In summary, difluoromethylthioester compounds as another important kind of organofluorine compounds are reported for the first time. Difluoromethylthioester compounds have been efficiently synthesized from cheap and abundant aldehydes including (hetero)aromatic aldehydes, aliphatic aldehydes, and *α*, *β*-unsaturated aldehydes. Featured by mild reaction conditions, good tolerance of functional groups, broad substrate scope, and especially no metal involving in the reaction, the approach has the potential to become an important tool for the late-stage functionalization of advanced synthetic intermediates, and should have many applications in medical chemistry. Preliminary mechanistic studies suggest that the protocol proceeds via a

radical process. The expansion of the transformations is currently underway and will be reported in the near future.

Acknowledgements

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Keywords: fluorine • difluoromethylthioesters • aldehydes • radical reactions

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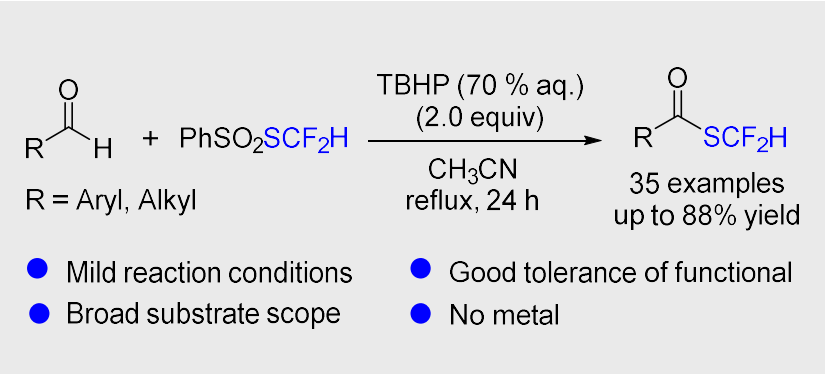

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Synthesis of Difluoromethylthioesters from Aldehydes

Difluoromethylthioester compounds have been efficiently synthesized from aldehydes for the first time. The synthetic method was featured by mild reaction conditions, good tolerance of functional groups, and broad substrate scope including (hetero)aromatic aldehydes, aliphatic aldehydes, and *α*, *β*-unsaturated aldehydes.