ChemComm

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/d0cc02912b

Received 22nd April 2020,
Accepted 23rd June 2020

DOI: 10.1039/d0cc02912b

rsc.li/chemcomm

Synthesis of difluoromethylselenoesters from aldehydes *via* a radical process†

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Difluoromethylselenoester compounds, another important kind of organoselenium compounds, are reported herein for the first time. They can be efficiently synthesized from aldehydes and BnSeCF$_2$H. The synthetic method features mild reaction conditions, broad substrate scope, good tolerance of functional groups, and importantly, no metal is involved in the reaction.

The past decade has witnessed tremendous growth of selenium chemistry, not only because selenium is an essential micronutrient for plants, microorganisms, animals, and humans,[1] but also because selenium compounds have great biological activities (*e.g.* antioxidant, antifatigue, and immunity activities)[2] and broad applications in materials fields, including alloys, photovoltaic products and nanotechnologies.[3] It is foreseeable that new selenium compounds and chemistry would emerge to reinvigorate these areas. Organoselenium compounds, particularly selenoesters (Fig. 1a), are important organic molecules which have shown extensive pharmaceutical activities such as anti-proliferation, anti-tumour and chemoprevention.[4] Selenoesters are also significant synthetic intermediates as acyl-radical precursors,[5] mild acyl-transfer agents, *etc.*[6,7] In addition, due to their promising photophysical properties, selenoesters have found wide applications in emissive LC displays, polarized organic lasers and anisotropic OLEDs.[8] Accordingly, the design and development of new selenoester compounds is greatly desirable in pharmaceutical and materials science.

The incorporation of fluorine atoms into molecules has become a common tactic to design novel lead compounds and modulate the properties of biologically active substances.[9] Over the past few decades, the difluoromethyl group has attracted great attention because: (1) it is a more lipophilic hydrogen-bonding donor than –OH and –NH;[10] (2) it can enhance the binding selectivity while fine-tuning the lipophilicity of the drug;[11] and (3) its electron-withdrawing capability can increase the drug's metabolic stability.[12] Recently, there has been considerable interest in the combination of difluoromethyl group and chalcogens, such as difluoromethoxyl (–OCF$_2$H) group[13] and difluoromethylthiol (–SCF$_2$H) group.[14] However, less research studies on difluoromethylseleno-containing (–SeCF$_2$H) compounds have been reported, probably due to the lack of an efficient method to synthesize them.[15]

According to the Hansch lipophilicity parameter values (π_R) of XCH$_3$ (X = O, S) and XCF$_2$H (Fig. 1b),[16] it can be speculated that the Hansch lipophilicity parameter value of the difluoromethylselenyl group (–SeCF$_2$H) is greater than that of the SeCH$_3$ group (π_R = 0.74). Therefore, SeCF$_2$H incorporation could increase the lipophilicity of parent compounds. To date, the reports are limited on difluoromethylselenoethers (Fig. 1c),[15] while difluoromethylselenoesters (Fig. 1d), which represent another important class of organoselenium compounds, have not been reported yet. In view of the potential properties of selenoesters and the difluoromethylselenyl group,

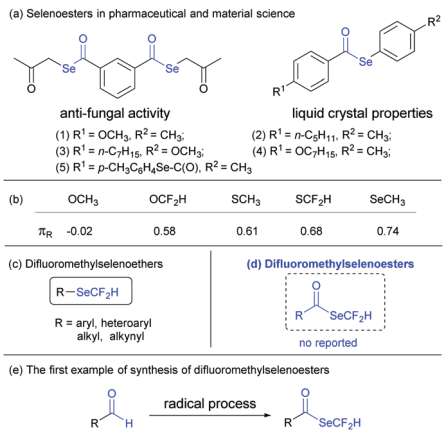

Fig. 1 Organoselenium compounds.

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† Electronic supplementary information (ESI) available: Detailed experimental procedures including spectroscopic and analytical data. CCDC compound **3g** (1985689) and compound **3ad** (1985690). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0cc02912b

the development of a new synthetic method for difluoromethylselenoesters would permit chemical derivatization of novel bioactive molecules and open a new window for selenium-related research and applications.

Aldehydes are abundant and inexpensive chemical materials and can easily generate the corresponding acyl radicals.[17a] Thus, we wondered whether the desired difluoromethylselenoesters could be directly formed by the coupling of the difluoromethylselenyl radical ($^{\bullet}SeCF_2H$) with aldehyde-derived acyl radicals (Fig. 1e).

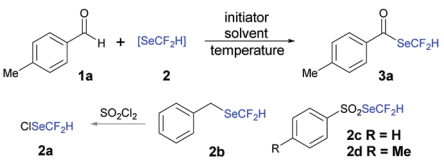
The study commenced with *p*-methylbenzaldehyde as an acyl radical precursor and di-*tert*-butyl peroxide (DTBP) as a radical initiator. Firstly, we used the most frequently used difluoromethylselenolation reagent, $ClSeCF_2H$ (**2a**), prepared from benzyl(difluoromethyl)selane (**2b**),[15d] to perform the reaction in CH_3CN at 80 °C for 24 h. Unfortunately, the desired difluoromethylselenoester **3a** was not observed. To our delight, instead of $ClSeCF_2H$ with Se-(difluoromethyl)-benzenesulfonoselenoate (**2c**), the reaction gave the desired product **3a** in 25% yield (Table 1, entry 2). A similar result was obtained with Se-(difluoromethyl)-4-methylbenzenesulfono selenoate (**2d**)[15h] as the difluoromethylselenolation reagent. To our surprise, the precursor of $ClSeCF_2H$, simple benzyl(difluoromethyl)selane (**2b**), afforded a superior yield (37%) (entry 4). Then with **1a** and **2b** as the model substrates, the initiator was screened. It was demonstrated that AIBN was better than the others, providing **3a** in 58% yield (entries 5–9). Meanwhile, the reaction without the initiator was carried out, and it did not afford any product, indicating the necessity of the initiator (entry 10). Subsequently, the optimization of the solvents showed that DCE was the best choice (entries 11 and 12). By increasing the amount of AIBN to 2.0 equivalents, the yield was improved to 84% (entry 13). Finally, the reaction temperature and atmosphere were investigated. It was demonstrated that a similar result could be obtained by lowering the temperature to 50 °C (entry 14). Interestingly, the yield could be improved to 90% under an argon atmosphere (entry 15). Accordingly, the optimized reaction conditions for the synthesis of **3a** were identified as follows: **1a** (0.75 mmol), **2b** (0.5 mmol), AIBN (1.0 mmol) and DCE (2.5 mL) at 50 °C under an argon atmosphere.

With the optimal conditions in hand, the substrate scope of this transformation was investigated (Scheme 1). A variety of aromatic aldehydes bearing either electron-rich groups or electron-deficient groups at different positions could react with **2b** smoothly to generate the corresponding difluoromethylselenoesters in moderate to excellent yields (**3a–3x**). The method proved to be compatible with various functional groups, such as alkyls (**3a–3e** and **3u**), halides (Cl, Br, I; **3f–3h**), phenyl (**3i**), ethers (**3j**, **3k**, and **3v–3x**), a protected phenolic hydroxyl group (**3l**), ester (**3m**), and a dimethylamino group (**3n**), and these functional groups can be further transformed in the synthesis. The structure of **3g** was confirmed by single-crystal X-ray diffraction analysis (see ESI†).

As illustrated in Scheme 2, we applied this method for the difluoromethylselenolation of naphthyl aldehydes. To our satisfaction, 1-naphthyl, 2-naphthyl and 1-bromine-2-naphthyl aldehydes successfully provided the desired products in good yields (**3aa–3ac**). As we know, heteroarenes are pharmaceutically important scaffolds.[18] Pleasingly, the reactions of **2b** with aldehydes containing indole, benzofuran, benzothiophene, pyrole, furan and thiophene motifs proceeded smoothly under the standard conditions (**3ad–3ai**). The structure of difluoromethylselenoester **3ad** was unambiguously confirmed using single-crystal X-ray diffraction.

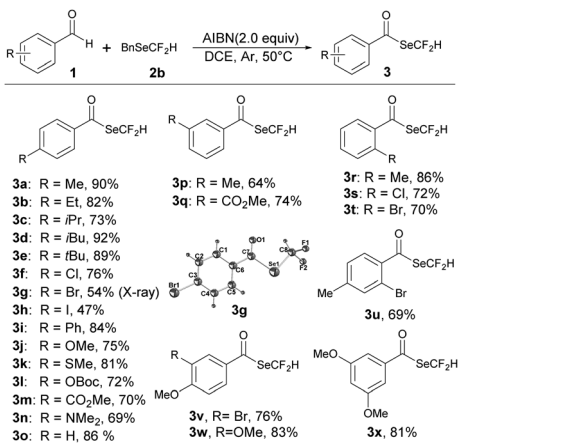
Encouraged by the success of (hetero)aromatic aldehydes, aliphatic aldehydes and α,β-unsaturated aldehydes were then

Table 1 Optimization of the difluoromethylselenolation reaction[a]

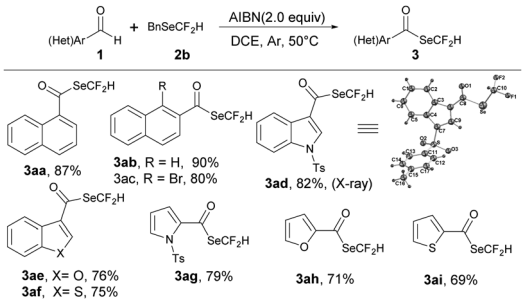


Entry	2	Initiator(equiv.)	Solvent	Temp. (°C)	Conv.[b] (%)	Yield[c] (%)
1	**2a**	DTBP(1.0)	CH_3CN	80	100	0
2	**2c**	DTBP(1.0)	CH_3CN	80	100	25
3	**2d**	DTBP(1.0)	CH_3CN	80	100	21
4	**2b**	DTBP(1.0)	CH_3CN	80	45	37
5	**2b**	TBHP(1.0)	CH_3CN	80	23	15
6	**2b**	H_2O_2(1.0)	CH_3CN	80	0	0
7	**2b**	$K_2S_2O_8$(1.0)	CH_3CN	80	0	0
8	**2b**	AIBN(1.0)	CH_3CN	80	67	58
9	**2b**	AMBN(1.0)	CH_3CN	80	61	54
10	**2b**	—	CH_3CN	80	0	0
11[d]	**2b**	AIBN(1.0)	Other solv.	80	<32	<27
12	**2b**	AIBN(1.0)	DCE	80	83	72
13	**2b**	AIBN(2.0)	DCE	80	100	84
14	**2b**	AIBN(2.0)	DCE	50	100	82
15[e]	**2b**	AIBN(2.0)	DCE	50	100	90

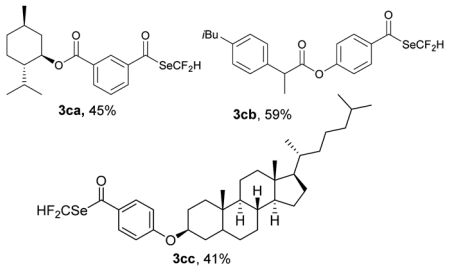
[a] Reaction conditions: **1a** (0.75 mmol), **2** (0.5 mmol), initiator, solvent (2.5 mL) and open to air for 24 h. [b] Based on **2**. [c] Yields of isolated **3a**. [d] Other solv.: $CHCl_3$ (27%), DMSO (0%), DMF (0%), toluene (18%), and THF (0%). [e] Under Ar (1 atmosphere). Conv. = conversion. DTBP = di-*tert*-butyl peroxide. TBHP = *tert*-butyl hydroperoxide (70 wt% in H_2O). H_2O_2 (30 wt% in H_2O). DCE = 1,2-dichloroethane. AIBN = 2,2′-azobis (2-methylpropionitrile). AMBN = 2,2′-azobis-isovaleronitrile.



Scheme 1 Difluoromethylselenolation of various aromatic aldehydes. Reaction conditions: **1** (0.75 mmol), **2b** (0.5 mmol), AIBN (1.0 mmol), and DCE (2.5 mL) under Ar at 50 °C for 24 h. Yields shown are those of isolated products.



Scheme 2 Difluoromethylselenolation of naphthyl aldehydes and heteroaromatic aldehydes. Reaction conditions: **1** (0.75 mmol), **2b** (0.5 mmol), AIBN (1.0 mmol), and DCE (2.5 mL) under Ar at 50 °C for 24 h. Yields shown are those of isolated products.

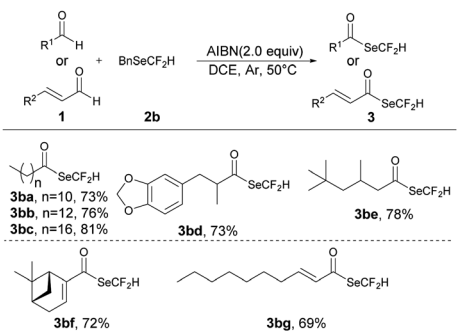


Scheme 4 Late-stage difluoromethylselenolation of aldehyde-containing bioactive molecules. Reaction conditions: **1** (0.75 mmol), **2b** (0.5 mmol), AIBN (1.0 mmol), and DCE (2.5 mL) under Ar at 50 °C for 24 h. Yields shown are those of isolated products.

investigated. Pleasingly, the reactivity of aliphatic aldehydes and α,β-unsaturated aldehydes was similar to (hetero)aromatic aldehydes. As summarized in Scheme 3, not only linear aliphatic aldehydes (**3ba–3bc**) but also branched aliphatic aldehydes (**3bd**, **3be**) were suitable substrates for this transformation. To further verify the efficacy of the method, α,β-unsaturated aldehydes were examined.[19] (−)-Myrtenal (**1bf**) and (*E*)-dec-2-enal (**1bg**) worked successfully to give the corresponding products in 72% and 69% yields, respectively. All the difluoromethylselenoesters synthesized are not sensitive to air, moisture or light at ambient temperature. The reaction of **1a** and **2b** was repeated 5 times, and the yield of **3a** remained in the range of 88–91%, verifying the stability and the reproducibility of this approach. The products can be easily purified using flash chromatography on silica gel.

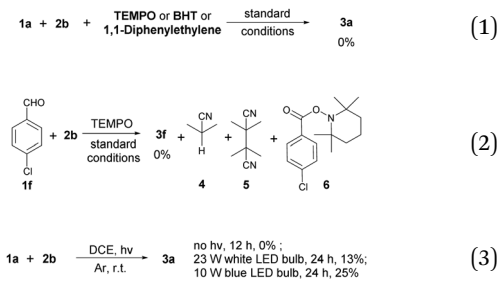
To demonstrate the synthetic application of this methodology, we employed it in the difluoromethylselenolation of complex aldehyde-containing molecules (Scheme 4). Known aldehyde-containing bioactive molecules, such as L-menthol derivative (**1ca**), ibuprofen derivative (**1cb**) and the cholesterol derivative (**1cc**) were all smoothly converted into their corresponding difluoromethylselenoesters (**3ca**, **3cb** and **3cc**), verifying that this approach can be used in the late-stage modification of drug molecules and advanced synthetic intermediates.

To gain insights into the reaction mechanism, we carried out a series of radical-trapping experiments. Firstly, no product



Scheme 3 Difluoromethylselenolation of aliphatic aldehydes and α,β-unsaturated aldehydes. Reaction conditions: **1** (0.75 mmol), **2b** (0.5 mmol), AIBN (1.0 mmol), and DCE (2.5 mL) under Ar at 50 °C for 24 h. Yields shown are those of isolated products.

3a was observed when the radical scavenger 2,2,6,6-tetramethyl piperidinyloxy (TEMPO), 2,6-di-*tert*-butyl-4-methylphenol (BHT) or 1,1-diphenylethylene was introduced into the reaction system under standard reaction conditions (eqn (1)). When TEMPO (1.0 equiv.) was introduced into the standard reaction system of **1f** and **2b**, isobutyronitrile (**4**), tetramethylsuccinonitrile (**5**) and the adduct **6** from the reaction of **1f** with TEMPO were detected using a high-resolution mass spectrometer (HRMS, see ESI†), while no **3f** was detected (eqn (2)). Isobutyronitrile (**4**) and tetramethylsuccinonitrile (**5**) could also be detected in the standard reaction system of **1a** and **2b** (see ESI†). These experiments indicated that the cyanoisopropyl radical and the acyl radical derived from aldehyde were probably involved in the reaction and the difluoromethylselenolation should undergo a radical path. Next, visible light-promoted experiments were implemented. Without the introduction of an initiator, the desired product **3a** could also be obtained in the presence of the irradiation of a 23 W white LED bulb or a 10 W blue LED bulb in 13% and 25% yields, respectively (eqn (3)). On the contrary, no reaction occurred without light. The photoreactions further supported the radical process of the transformation.



Based on these results and the related literatures,[17,20] a plausible mechanism for the synthesis of difluoromethylselenoesters is proposed as shown in Fig. 2. Initially, AIBN is thermally decomposed into a cyanoisopropyl radical, which abstracts a hydrogen atom from the aldehyde (**1**) to generate an acyl radical (**A**) and isobutyronitrile (**4**).[20b] Cyanoisopropyl radicals can also undergo homocoupling to generate tetramethylsuccinonitrile (**5**).[20e] Then **A** reacts with **2b** to form the desired product **3**. We tried to ascertain the product derived from the benzyl group of **2b**, but complicated results have been

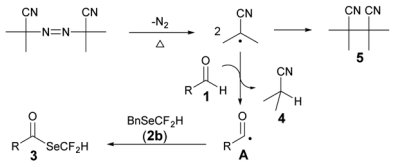


Fig. 2 Plausible mechanism.

obtained, and the relative research studies are ongoing and further detailed mechanism investigations are underway.

In summary, difluoromethylselenoester compounds, another novel and promising class of selenoester compounds, are reported for the first time. They can be efficiently synthesized from aldehydes with simple $BnSeCF_2H$. This approach features mild reaction conditions, broad substrate scope, good tolerance of functional groups, and importantly, no metal is involved in the reaction. The difluoromethylselenolations of several aldehyde-containing bioactive derivatives have been realized; thus, this approach has the potential to be an important tool for the late-stage modification of aldehyde-containing drug molecules and advanced synthetic intermediates.

We are grateful for financial support from National Natural Science Foundation of China (No. NSFC-21572178, NSFC-21702162 and NSFC-21971206).

Conflicts of interest

There are no conflicts to declare.

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