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Efficient capture of difluorocarbene by pyridinium 1,4-zwitterionic thiolates: A concise synthesis of difluoromethylene-containing 1,4-thiazine derivatives

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ABSTRACT

A practical method for the construction of difluoromethylene-containing 1,4-thiazine moieties using readily available diethyl bromodifluoromethanephosphonate ($BrCF_2PO(OEt)_2$) as difluorocarbene precusor has been developed. This transformation features the efficient capture of difluorocarbene by pyridinium 1,4-zwitterionic thiolates. A series of structurally novel and functionalized difluoromethylene-containing 1,4-thiazine derivatives were thus synthesized in good yields.

1,4-Thiazine is a ubiquitous heterocyclic motif which exists in a broad range of pharmaceutical molecules (Fig. 1) [1,2]. For example, Chlorpromazine is the first worldwide used antipsychotic drug [2], nifurtimox is an anthelmintic for trypanosoma cruzi and has a potential utility for neuroblastoma cell research [3]. Moreover, it is widely known that the introduction of fluorine-containing moieties, for instance, difluoromethylene CF_2 and in particular difluorothiomethylene SCF_2, can usually enhance the pharmaceuticals' biological and physiological activities such as metabolic property, lipophilicity, and oxidative stability (Fig. 1) [4–12]. Accordingly, a practical method that can incorporate both two important moieties 1,4-thiazine and difluoromethylene in a single step will be appealing and of great value.

However, to the best of our knowledge, only a few synthetic methods have been developed for the construction of difluorothiomethylene-containing heterocyclic compounds. Typical synthetic routes include: DBU-catalyzed [4 + 2] annulation between *gem*–difluoroolefins and 2-mercaptobenzaldehydes (Scheme 1A, a) [13]; cyclization of difluorothiomethylene-containing precursors, which proceeded *via* a radical addition of difluoromethyl xanthate to terminal alkenes [14] or a visible-light-induced arylthiofluoroalkylations of unactivated heteroarenes and alkenes (Scheme 1A, b) [15]; three-component reaction of 2′-aminochalcone, sulfur, and $ClCF_2CO_2Na$ in the presence of TEMPO, which proceeded through a radical anti-Michael addition and nucleophilic addition of difluorocarbanion to amide (Scheme 1A, c) [16].

Alternatively, we envisioned that those structures could be accessible *via* a difluorocarbene capture reaction of pyridinium 1,4-zwitterionic thiolates, because they have been proven to be versatile reagents that can proceed a series of novel reactions. For example, Cheng, Zhai *et al.* recently reported several beautiful works in which pyridinium 1,4-zwitterionic thiolates played as either five-membered or three-membered synthons to construct varied sulfur-containing heterocycles [17–25]. Moreover, employing difluorocarbene ($:CF_2$) as difluoromethylene source has become a powerful synthetic platform in recent years [26,27]. Several strategies, including reacting with a nucleophile and an electrophile [28–40], Wittig reaction with carbonyls [41–44] and [2 + 1] cycloaddition with alkenes or alkynes [45] have been established to incorporate difluoromethylene moiety into a wide spectrum of organic molecules (Scheme 1B). Based on the above-mentioned works and our continuous interest in difluorocarbene-involved transformations [46,47], herein we present a cyclization of pyridinium

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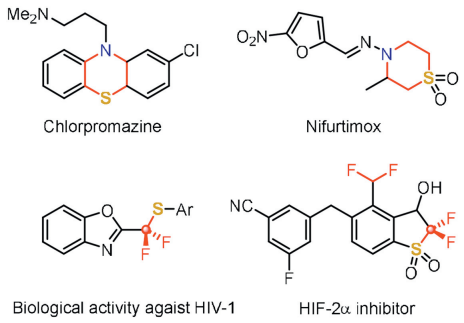
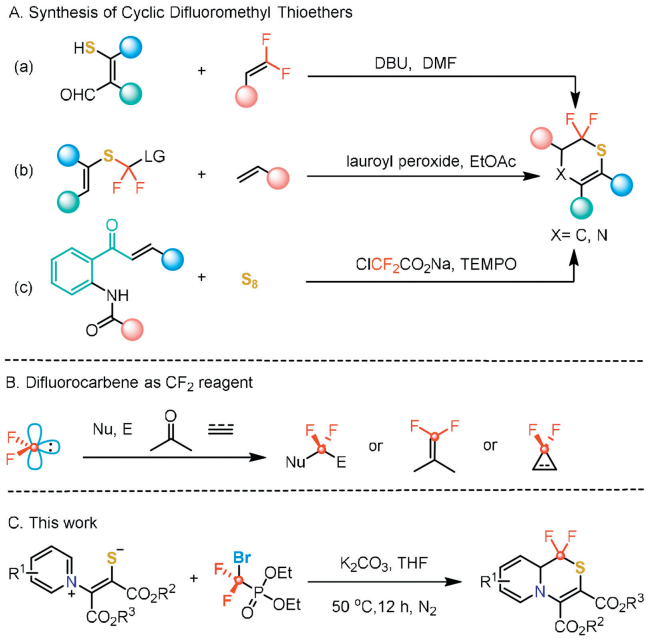


Fig. 1. Drug molecules containing -SCF_2- scaffolds and chemical medications contains 1,4-thiazine.



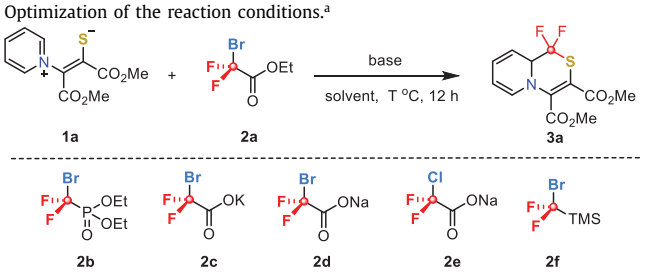
Scheme 1. Reaction modes of difluorocarbene.

1,4-zwitterionic thiolates with difluorocarbene to rapidly and efficiently synthesize the target difluorothiomethylene-containing 1,4-thiazine derivatives (Scheme 1C).

We employed (*Z*)-1,4-dimethoxy-1,4-dioxo-3-(pyridin-1-ium-1-yl)but-2-ene-2-thiolate **1a** as model substrate and $BrCF_2CO_2Et$ **2a** as difluorocarbene source to explore the feasibility of our design (Table 1). Gratifyingly, when **1a** and 3.0 equiv. of **2a** were treated with 3.0 equiv. of base K_2CO_3 in CH_3CN at 80 °C, the desired product **3a** was obtained in 58% isolated yield (entry 1). Then different bases (Na_2CO_3, K_3PO_4, Cs_2CO_3, $NaHCO_3$) were evaluated (entries 2–5) and K_2CO_3 was proven to be optimal. To our delight, when the temperature was lowered to 50 °C and THF was used instead of CH_3CN as solvent, the yield could be further improved to 78% (entries 6–11). Subsequent screening of other difluoromethylene-containing reagents such as $BrCF_2PO(OEt)_2$, $BrCF_2COOK$, $BrCF_2COONa$, $ClCF_2COONa$, and $TMSCF_2Br$ showed that an excellent 93% yield was achieved when employing $BrCF_2PO(OEt)_2$ as difluorocarbene source (entries 12–16). Further studies showed that either reacting under air (entry 17) or reducing the amount of $BrCF_2PO(OEt)_2$ (entry 18) resulted in decreased yields.

With the optimal reaction conditions in hand (Table 1, entry 12), we then investigated the substrate scope of pyridinium 1,4-zwitterionic thiolates. As shown in Scheme 2, the reaction exhibited good functional group compatibility. For example, a series of

Table 1
Optimization of the reaction conditions.[a]

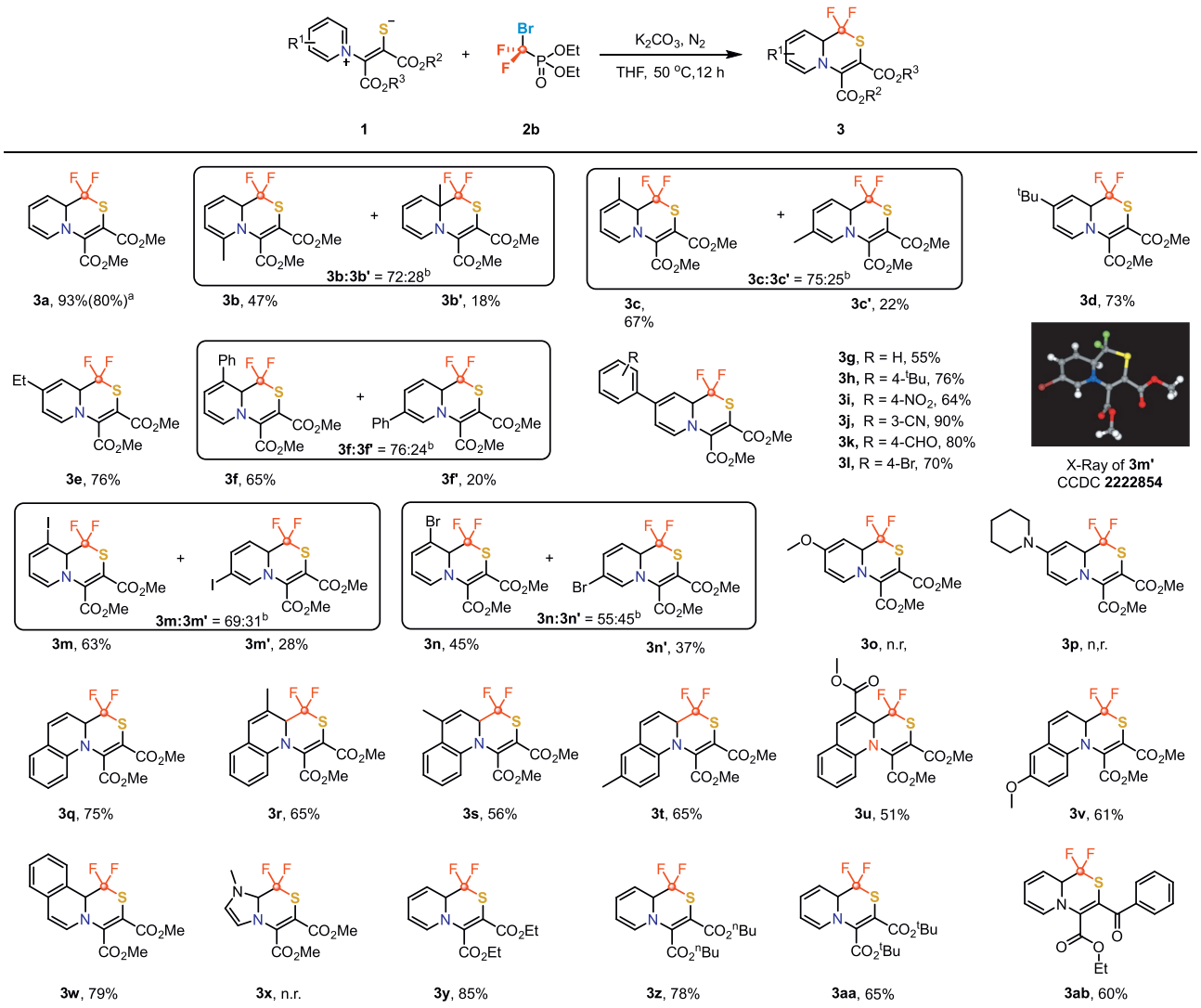


Entry	2	Base	Solvent	*T* (°C)	Yield (%)
1	**2a**	K_2CO_3	CH_3CN	80	58
2	**2a**	Na_2CO_3	CH_3CN	80	Trace
3	**2a**	K_3PO_4	CH_3CN	80	50
4	**2a**	Cs_2CO_3	CH_3CN	80	33
5	**2a**	$NaHCO_3$	CH_3CN	80	Trace
6	**2a**	K_2CO_3	CH_3CN	70	53
7	**2a**	K_2CO_3	CH_3CN	60	62
8	**2a**	K_2CO_3	DCE	60	Trace
9	**2a**	K_2CO_3	THF	60	70
10	**2a**	K_2CO_3	THF	50	78
11	**2a**	K_2CO_3	THF	40	50
12	**2b**	K_2CO_3	THF	50	93
13	**2c**	K_2CO_3	THF	50	Trace
14	**2d**	K_2CO_3	THF	50	Trace
15	**2e**	K_2CO_3	THF	50	Trace
16	**2f**	K_2CO_3	THF	50	n.r.
17[b]	**2b**	K_2CO_3	THF	50	62
18[c]	**2b**	K_2CO_3	THF	50	56

[a] Reaction conditions: **1a** (0.2 mmol), **2** (3 equiv.), base (3 equiv.), solvent (2 mL) under N_2 atmosphere for 12 h, isolated yield; n.r. = no reaction.
[b] Air.
[c] **2a** (2 equiv.).

aliphatic and aromatic substituents on different positions of the pyridinium rings all did not affect the efficiency of the reaction, affording the target products (**3b**-**3l**) in moderate to good yields.

However, the regioselectivities of the reaction were moderate, for instance, 2-methyl substituted substrate gave a mixture of two regioisomers **3b** and **3b′** with a 72:28 ratio. Similar results were also observed when 3-methyl or 3-phenyl substituted substrates were employed (**3c** and **3c′**, **3f** and **3f′**). 4-Alkyl substituted, as well as 4-aryl substituted substrates bearing a series of electron-donating and electron-withdrawing substituents such as *tert*-butyl, nitryl, cyano, formyl, and halogens on the phenyl rings all reacted very well, furnishing the single isomers in good yields (**3d, 3e, 3g–3l**). Besides aliphatic and aromatic substituents, other functionalities were also compatible with the reaction. For example, 3-iodo/bromopyridinium thiolates both afforded the target products in good yields with 69:31 and 55:45 regioselectivities, respectively (**3m** and **3m′**, **3n** and **3n′**). The exact structure of compound **3m′** was unequivocally determined by single crystal X-ray diffraction. However, 4-methoxy- and 4-piperidinylpyridinium thiolates were failed to give the desired products, this may be attributed to that 4-methoxy- and 4-piperidinyl groups can stabilize the carbocation in pyridinium through resonance and hence decrease their electrophilicity (**3o** and **3p**). Next, we explored the scope of different benzo pyridinium thiolates. For example, quinolinium 1,4-zwitterionic thiolates and its derivatives bearing different substituents such as alkyl, carboxylate and methoxy all smoothly cyclized under the standard conditions and furnished the corresponding products in 51%–75% yield (**3q**-**3v**). Besides, isoquinolinium 1,4-zwitterionic thiolates was also compatible and afforded the target product **3w** in 79% yield, albeit *N*-methylimidazolium thiolate did not give the cyclization product **3x**. Finally, the scope of the ester groups was studied and the resulted showed that ethyl, *n*-butyl, and more sterically hindered *tert*-butyl esters were

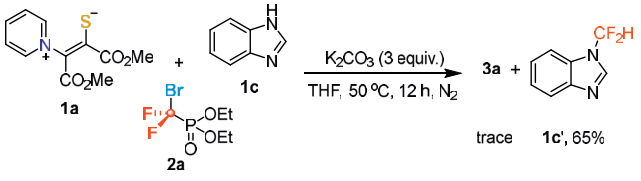


Scheme 2. Substrate scope of pyridinium 1,4-zwitterionic thiolates **1**. Reaction condition: **1** (0.2 mmol), **2b** (0.6 mmol), THF (2 mL), K_2CO_3 (0.6 mmol), under N_2 atmosphere at 50 °C for 12 h; Isolated yields. [a] The reaction was conducted on the gram scale. [b] Determined by ^1H NMR.

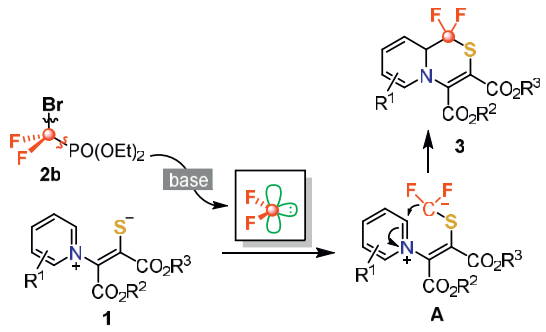
all good candidates for this reaction (**3y**–**3aa**). Pyridinium thiolate bearing an ester and a ketone group was also found to be compatible, affording the desired product **3ab** in 60% yields.

To better understand the mechanism of this reaction, we carried out a control experiment. When the difluorocarbene capture reagent benzimidazole (**1c**) was added to the reaction system, 1-(difluoromethyl)-1*H*-benzo[*d*]imidazole (**1c'**) was isolated in good yields, while product **3a** was not detected (Scheme 3), which suggests that difluorocarbene was generated in our transformations.

On the basis of our experimental results and in combination with previous reports on difluoromethylation [46,47], a plausible mechanism is proposed in Scheme 4. Difluorocarbene, which is generated *in situ* from precursor compound **2b** in the presence of a base, was first attacked by the sulfur anion in pyridinium 1,4-



Scheme 3. Control experiment.



Scheme 4. Plausible mechanism.

zwitterionic thiolates **1** to form intermediate **A**. Subsequent intramolecularly nucleophilic addition of the difluoro-carbanion to the iminium double bond hence furnishes the final product **3**.

In summary, we have successfully developed a transition metal-free and additive-free practical method for the synthesis of a series of functionalized difluoromethylene-containing 1,4-thiazine derivatives using readily available diethyl bromodifluoromethanephosphonate ($BrCF_2P(O)(OEt)_2$) as difluorocarbene source. The *in situ* generated difluorocarbene was efficiently captured by pyridinium

1,4-zwitterionic thiolates, thus incorporating the difluoromethylene motif in a simple and atom-economic manner. Further studies on the highly efficient incorporation of difluorocarbene by employing different kinds of substrates and precursors are underway in our group.

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.

Acknowledgments

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2023.108937.

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