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# Difluoromethanesulfonyl hypervalent iodonium ylides for electrophilic difluoromethylthiolation reactions under copper catalysis

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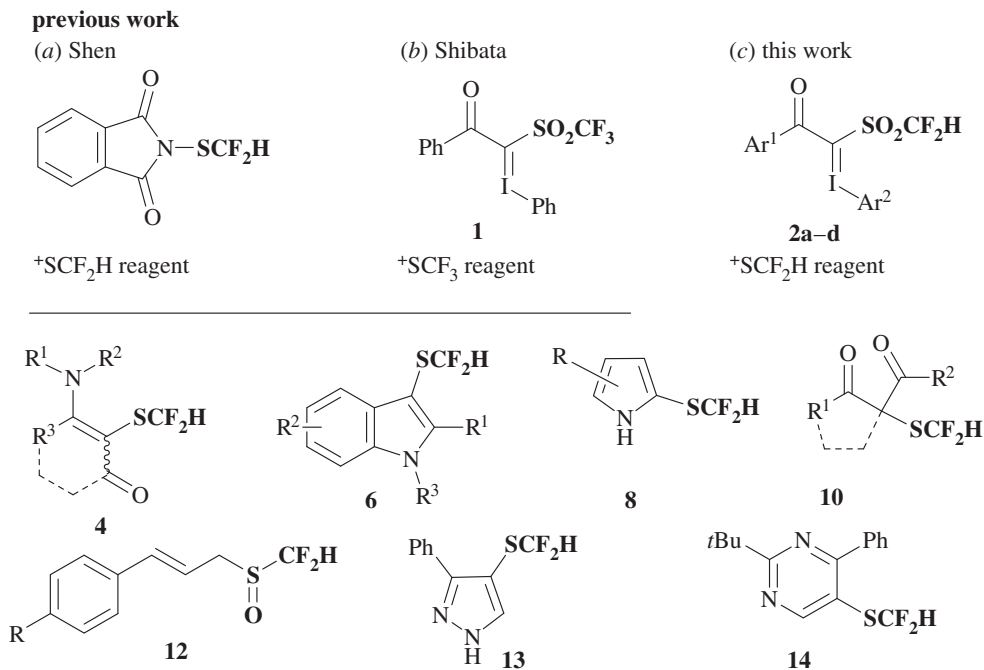
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Difluoromethanesulfonyl hypervalent iodonium ylides **2** were developed as electrophilic difluoromethylthiolation reagents for a wide range of nucleophiles. Enamines, indoles,  $\beta$ -keto esters, silyl enol ethers and pyrroles were effectively reacted with **2** affording desired difluoromethylthio (SCF<sub>2</sub>H)-substituted compounds in good to high yields under copper catalysis. The reaction of allyl alcohols with **2** under the same conditions provided difluoromethylsulfinyl (S(O)CF<sub>2</sub>H) products in good yields. The difluoromethylthiolation of enamines is particularly effective with wide generality, thus the enamine method was nicely extended to the synthesis of a series of difluoromethylthiolated cyclic and acyclic  $\beta$ -keto esters, 1,3-diketones, pyrazole and pyrimidine derivatives by a consecutive, two-step one-pot reaction using **2**.

## 1. Introduction

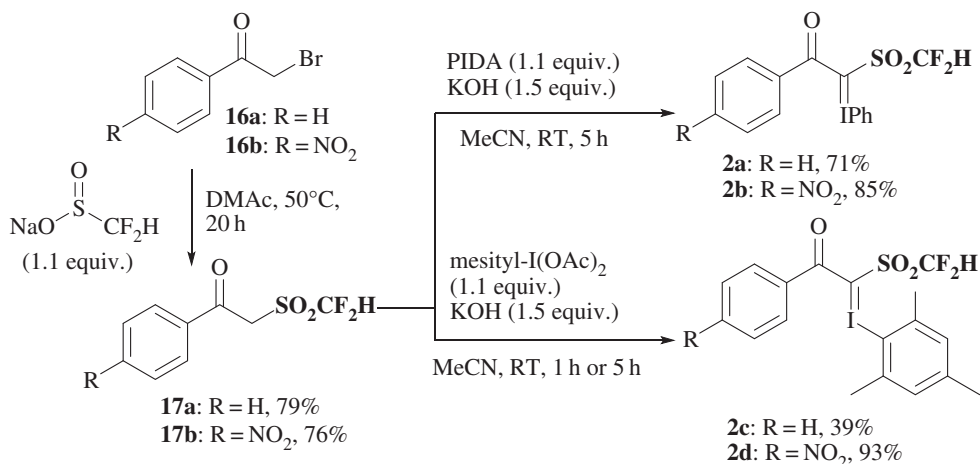
Fluorine (F) and sulfur (S) atoms have been individually recognized over the past couple of decades to be important structural elements with biological activities in drugs [1–10]. These facts, together with the recent successful observation on the market that the trifluoromethyl (CF<sub>3</sub>) group is frequently found in pharmaceuticals and agrochemicals [11–15], have led medicinal chemists to explore the use of the trifluoromethylthio (SCF<sub>3</sub>) group as a strategic functional component to assist in drug discovery [16–38]. In recent years, more than a



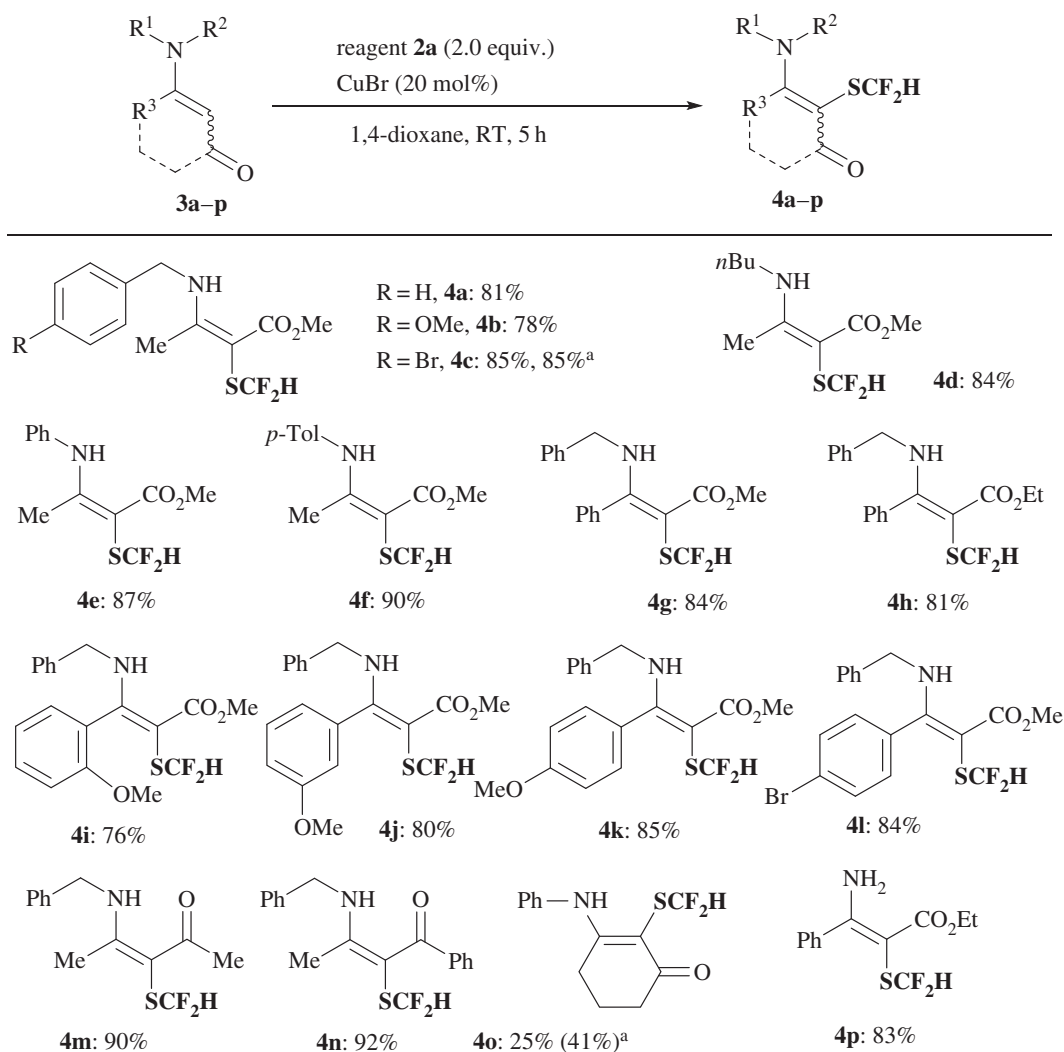
**Figure 1.** Previous studies on (a) +SCF<sub>2</sub>H reagent, (b) +SCF<sub>3</sub> reagent and (c) hypervalent iodonium ylides as +SCF<sub>2</sub>H reagents.

dozen attractive synthetic methods for introduction of the SCF<sub>3</sub> group into target compounds have been successively reported [16–38]. In this context, the difluoromethylthio group (SCF<sub>2</sub>H) has emerged as a next potential subject in this field. While SCF<sub>3</sub> is entirely lipophilic, the SCF<sub>2</sub>H group has the potential to be a weak hydrogen-bonding donor, which results in a suitable hydrophilic/hydrophobic balance of SCF<sub>2</sub>H-substituted molecules [39–42]. Thus, incorporation of SCF<sub>2</sub>H into biologically active molecules should permit the efficient design of novel, viable drug candidates. There are several synthetic approaches available for SCF<sub>2</sub>H-substituted compounds [43–59], such as nucleophilic reaction of appropriate thiolates to difluoromethyl carbene [43–53] and electrophilic or radical difluoromethylation of thiolates [54–56]. These methods rely upon the construction of a bond between S and CF<sub>2</sub>H, and therefore have some limitations, although recently Goossen *et al.* provided a solution via copper-mediated difluoromethylation of organothiocyanates [57,58]. Impressively, Shen and co-workers [60] reported Sandmeyer-type direct diifluoromethylthiolation using an *N*-heterocyclic carbene difluoromethylthiolated silver complex to provide aryl SCF<sub>2</sub>H compounds. The method is an ideal approach for introducing SCF<sub>2</sub>H, but the substrate scope is limited to diazonium salts. The same group reported the first shelf-stable electrophilic difluoromethylthiolation reagent, *N*-difluoromethylthiophthalimide or the Shen reagent (figure 1a) [61].

The Shen reagent is efficient, but new reagents and more methods to expand the accessibility to a wide variety of SCF<sub>2</sub>H compounds are continuously required. Incidentally, we reported in 2013 that trifluoromethanesulfonyl (SO<sub>2</sub>CF<sub>3</sub>) hypervalent iodonium ylide **1** is an efficient reagent for the electrophilic trifluoromethylthiolation reaction (figure 1b) [62]. Despite its carbon-SO<sub>2</sub>CF<sub>3</sub> structure, a reactive SCF<sub>3</sub> species is unexpectedly, but effectively released from **1** via C–S bond cleavage under copper catalysis allowing it to be transferred into a wide variety of nucleophilic substrates including enamines, indoles, β-keto esters, pyrroles [63], allylsilanes, silyl enol ethers [64], allyl alcohols and boronic acids [65]. Inspired by this powerful reactivity and wide substrate generality and linked to the mechanistic uniqueness of iodonium ylide reagent **1**, we describe herein an investigation of novel shelf-stable electrophilic difluoromethylthiolation reagents **2** and their reactivity towards a variety of nucleophiles (figure 1c). Difluoromethanesulfonyl (SO<sub>2</sub>CF<sub>2</sub>H) hypervalent iodonium ylides **2** were found to be useful for electrophilic difluoromethylthiolation of a variety of nucleophiles including enamines **3**, indoles **5**, pyrroles **7** and β-keto esters **9** to provide corresponding SCF<sub>2</sub>H products **4**, **6**, **8** and **10**. The reaction of allyl alcohols **11** with **2** under the same conditions provided difluoromethylsulfinyl (S(O)CF<sub>2</sub>H) products **12**, instead of SCF<sub>2</sub>H products, in good yields. These methods can be applied to the synthesis of a series of difluoromethylthiolated cyclic and acyclic β-keto esters, 1,3-diketones **10**, pyrazole **13** and pyrimidine **14** by a consecutive, two-step one-pot reaction using **2** under an enamine strategy. The reactivity and reaction mechanism of **2** are discussed.

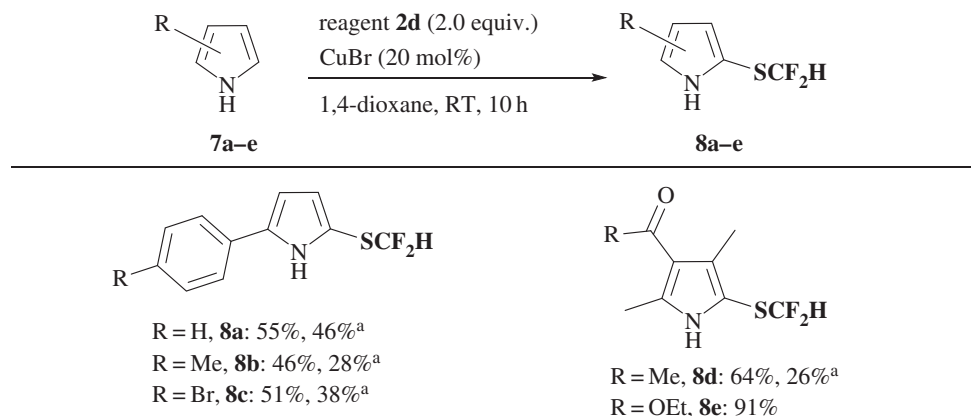


**Scheme 1.** Preparation of difluoromethylthiolation reagents **2**.

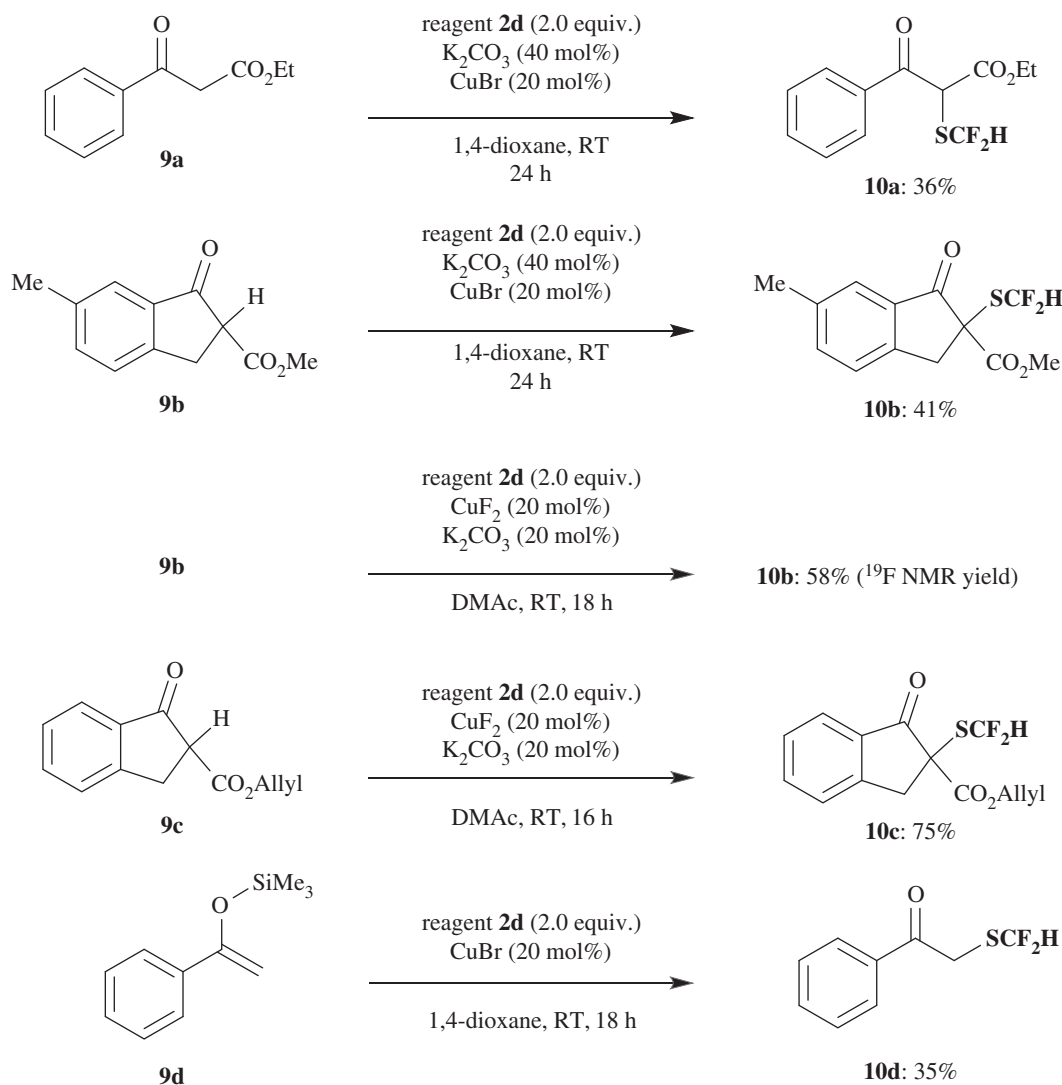


**Scheme 2.** Difluoromethylthiolation of enamines **3**. Superscript 'a' denotes reagent **2d** was used instead of **2a**.





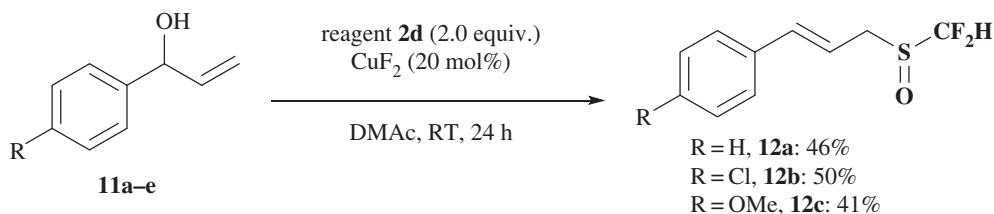
**Scheme 4.** Difluoromethylthiolation of pyrroles **7**. Superscript 'a' denotes reagent **2a** was used.



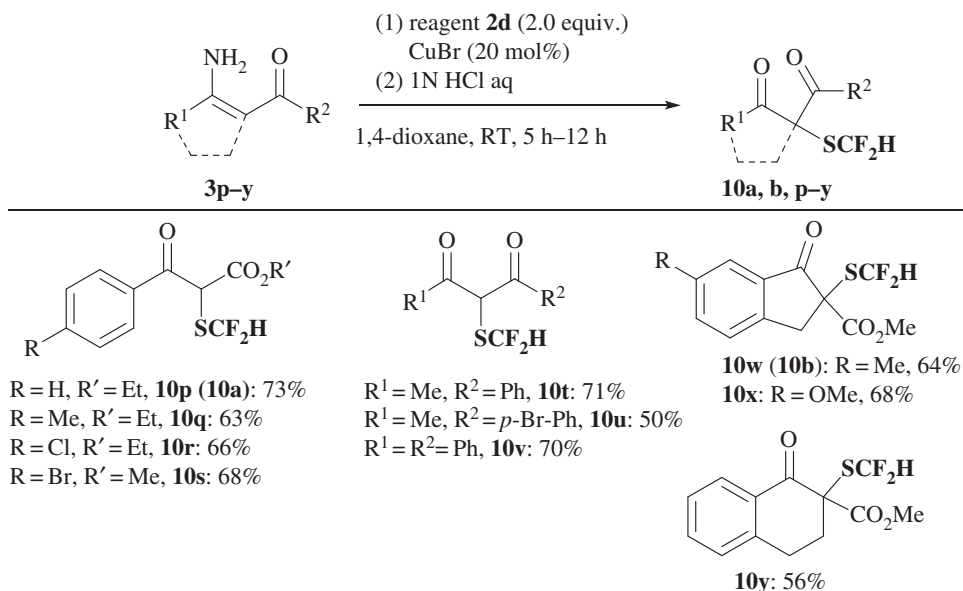
**Scheme 5.** Difluoromethylthiolation of  $\beta$ -keto esters **9a–c** and silyl enol ether **9d**.

in moderate yield (46%) via a [2,3]-sigmatropic rearrangement, instead of an SCF<sub>2</sub>H compound. Both the electron-donating (OMe) and electron-deficient (Cl) groups were applicable in the reaction (scheme 6).

The difluoromethylthiolation reaction by **2** is particularly useful for the reaction of enamines. It should be noted that the difluoromethylthiolation of enamines, i.e. the enamine method, can be expanded to the



**Scheme 6.** Reaction of allyl alcohols **11** with **2a**.

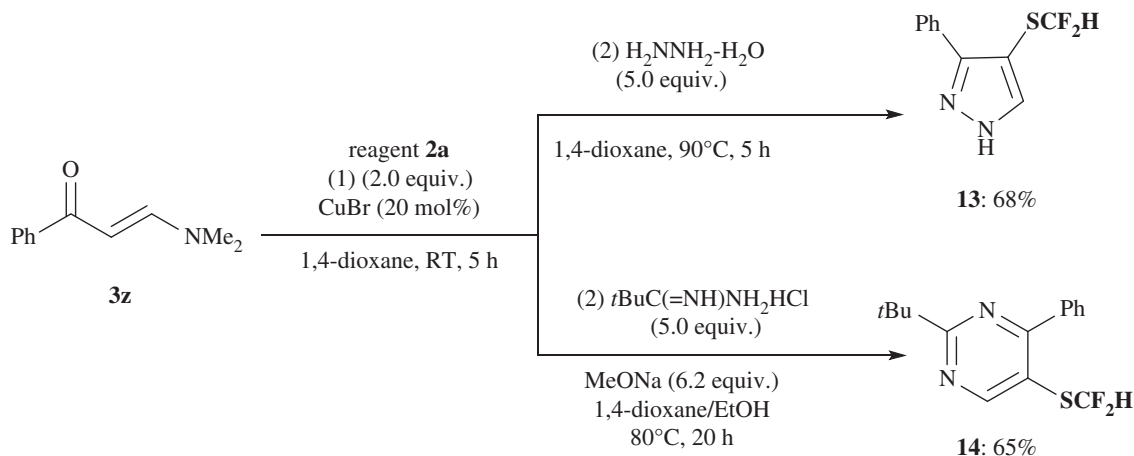


**Scheme 7.** Enamine method: two-step, one-pot synthesis of difluoromethylthiolated  $\beta$ -keto esters and 1,3-diketones **10** from  $\text{NH}_2$ -enamines **3p-y**.

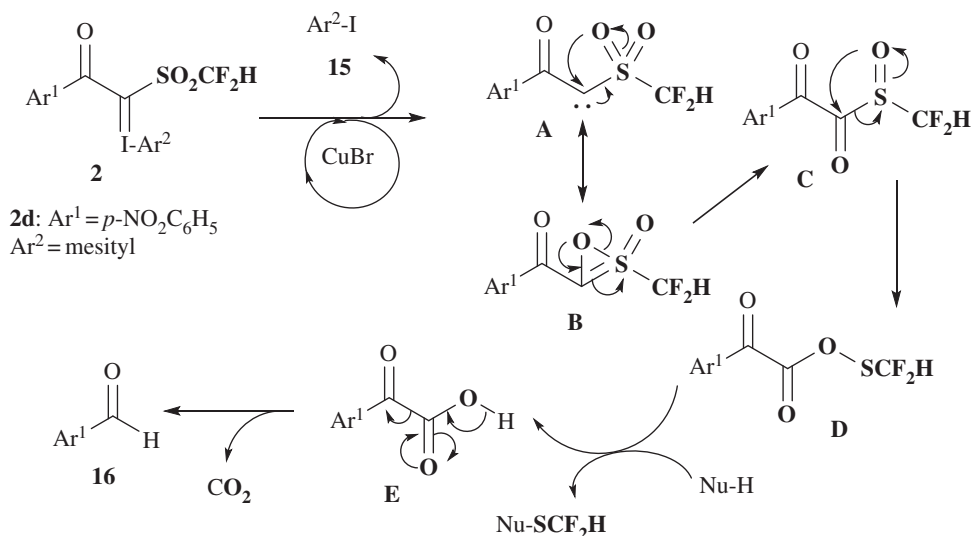
synthesis of  $\alpha$ -SCF<sub>2</sub>H- $\beta$ -keto esters and  $\alpha$ -SCF<sub>2</sub>H-1,3-diketones by a one-pot combination of reactions that involves difluoromethylation of unprotected,  $\text{NH}_2$ -enamine esters and enamine ketones **3p-y** with **2a** and subsequent hydrolysis (scheme 7). A series of acyclic and cyclic  $\alpha$ -SCF<sub>2</sub>H- $\beta$ -ketoesters and  $\alpha$ -SCF<sub>2</sub>H-1,3-diketones with a variety of substituents were obtained in high yields (**10a, b, p-y**: 63–73%). This enamine method has the advantage of higher yields relative to the direct reaction with  $\beta$ -keto esters. More importantly, acyclic  $\alpha$ -SCF<sub>2</sub>H,  $\beta$ -keto esters and ketones are not prepared using the Shen reagent [61], presumably due to the lower reactivity of acyclic substrates than cyclic ones (**9a-c**; scheme 5).

The enamine method was further extended to allow the synthesis of biologically attractive SCF<sub>2</sub>H-substituent heterocycles of pyrazole and pyrimidine by a similar two-step, one-pot, consecutive reaction procedure (scheme 8). First, enamine ketone **3z** was treated with **2a** in the presence of CuBr in dioxane at room temperature for 5 h. The addition of hydrazine monohydrate (5.0 equiv.) followed by heating and cyclohydration produced 4-difluoromethylthiolated pyrazole **13** in 68% yield. Similarly, the difluoromethylation of **3z** with **2a** followed by treatment with *tert*-butylcarbamidine hydrochloride (5.0 equiv.) and sodium methoxide (6.2 equiv.) under heated conditions gave 5-difluoromethylthiolated pyrimidine **14** in 65% yield.

A proposed reaction mechanism of difluoromethylthiolation by reagent **2** is postulated in scheme 9. This mechanism is principally the same as a previous consecutive reaction mechanism [62,63] by SCF<sub>3</sub>-reagent **1** involving successive (i) copper-catalyzed carbene-generation **A**, (ii) oxathiirene-2-oxide formation **B**, (iii) rearrangement to sulfoxide **C**, and (iv) collapse to thioperoxoate **D**. Hence, the SCF<sub>2</sub>H thioperoxoate **D** is likely to be an actual species for electrophilic difluoromethylthiolation of nucleophiles via decarboxylation of **E**. Detection of the residues, Ar<sup>2</sup>-I **15** (Ar<sup>2</sup> = mesityl) and Ar<sup>1</sup>CHO **16** (Ar<sup>1</sup> = *p*-NO<sub>2</sub>Ph) after the reaction with reagent **2d**, together with the previous mechanistic investigation using SCF<sub>3</sub>-reagent **1** [62,63], strongly support the reaction mechanism shown in scheme 9 (also see electronic supplementary material, scheme S3).



**Scheme 8.** Enamine method: two-step, one-pot synthesis of difluoromethylthiolated pyrazole **13** and pyrimidine **14** from enamine **3z**.



**Scheme 9.** The proposed reaction mechanism.

The roles of copper catalysts, CuF<sub>2</sub> and CuBr, depending on the substrates are not known. The Lewis acid centre of CuF<sub>2</sub> is harder than the Lewis acid centre of CuBr; since Cu(II) is harder than Cu(I), F<sup>-</sup> is harder than Br<sup>-</sup>. The reaction mechanism in scheme 9 includes sulfur atoms with different oxidation states with different softness and hardness (from soft to hard: S, S(O) and SO<sub>2</sub>) [67], thus the catalyst of CuF<sub>2</sub> or CuBr might also activate the different stage of each transition state. The more clear explanation should be required based on the detailed study such as molecular calculations.

### 3. Conclusion

In conclusion, the preparation and application of novel electrophilic difluoromethylthiolation reagents **2a–d** have been developed. Reagents **2** were found to be useful for the difluoromethylthiolation of a wide range of enamines, indoles, pyrroles and β-keto esters. Allylic alcohols were also reacted with **2** to provide allylic S(O)CF<sub>2</sub>H compounds via sigmatropic rearrangement. The difluoromethylthiolation of enamines (enamine method) can be widely extended to the synthesis of a variety of SCF<sub>2</sub>H-β-keto esters, 1,3-diketones, pyrazole and pyrimidine under a two-step one-pot procedure. High yields are obtained with a wide substrate scope and the reactions proceed at room temperature. This should be compared with Shen's recent papers on SCF<sub>2</sub>H transfer, which need elevated temperatures and prolonged reaction times [61] or stoichiometric amounts of a silver complex. Besides, the access to the SCF<sub>2</sub>H-β-keto esters

and 1,3-diketones is more general by our reagents than the Shen reagent [61]. Because the fluorine often induces some expectation and something interesting [9,10,68–72], our new SCF<sub>2</sub>H reagents would be efficient tools for the development of novel drugs and functional materials. Further investigation of reagent **2** for the difluoromethylthiolation of other substrates, such as heteroatom nucleophiles (N-, S- or P-nucleophiles), is underway.

**Data accessibility.** The datasets supporting this article have been uploaded as part of the electronic supplementary material.

**Authors' contributions.** S.A., O.M. and M.T. conducted and analysed the experiments and compounds. M.S. conducted X-ray crystallographic analysis and gave useful discussion. N.S. designed, directed the project and wrote the manuscript with contributions from S.A., O.M., M.T. and M.S. All authors contributed to discussions and gave final approval for publication.

**Competing interests.** We declare we have no competing interests.

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