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Defluorinative thio-functionalization: direct synthesis of methyl-dithioesters from trifluoromethylarenes†

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A new functional group transformation allowing the synthesis of methyl-dithioesters from readily available trifluoromethyl arenes *via* defluorinative functionalization has been developed. This microwave-assisted method is operationally simple, rapid, and eliminates the need for pre-functionalization while accommodating a broad range of functional groups. In addition, it does not rely on highly odorous thiol sources, and utilizes the commercially available reagent BF_3SMe_2 complex as a multifunctional Lewis acid/sulfur source/defluorination and demethylation agent. Finally, this approach is suitable for late-stage functionalizations, as shown by the transformation of pharmaceuticals leflunomide, flufenamic acid and celecoxib into novel methyl-dithioester derivatives.

Trifluoromethyl (CF_3)-substituted arenes are common structural motifs in many biologically active molecules as the CF_3 substituent often has a profound influence on their biological, chemical and physical characteristics.[1] As a consequence, CF_3 groups can be found in a number of drugs such as celecoxib, flufenamic acid and leflunomide.

In addition to its interesting properties, the CF_3-group has found increasing utility as a latent synthetic handle. Despite the high activation energy of the C–F bond posing a significant synthetic challenge, recent advances have allowed the group to be seen as a precursor for a range of different transformations.[2] These approaches include Lewis acids activation,[2c,d] transition metal catalysis[2e] and photo/electrochemical acitivation.[2f] However, the incorporation of sulfur nucleophiles has only rarely been reported[3] and, moreover, these methods all require the use of highly odorous thiols or sulfides,[3a] specialized substrates[3b] complex reaction conditions[3c] (Fig. 1), or report very few examples of sulfur transformations.[3d–g] We have previously disclosed the use of BF_3SMe_2 complex as a convenient and non-odorous Lewis acid and thiomethyl source.[4] Noting that many CF_3 functionalization approaches hinge on a Lewis acid/nucleophile combination, we speculated that BF_3SMe_2 might also promote C–F activation and subsequent thiomethyl incorporation. Given the propensity for the CF_3-group to undergo multiple defluorination events,[2] a key potential issue was identifying selective reaction conditions.

Pleasingly, when trifluorotoluene (**1a**) was treated with an excess of BF_3SMe_2 at elevated temperatures, a single main product was formed that was ultimately identified as the methyl-dithioester **1b** (Table 1). Importantly, the transformation of an aryltrifluoromethyl group into a dithioester is, to the best of our knowledge, unknown in the literature.

The methyl-dithioester group is a versatile synthetic intermediate that has been employed in the synthesis of a variety of heterocycles,[5] as a heterodieneophile,[6] and a key step in the synthesis of a shikimic acid derivative[7] and the potassium channel activator aprikalim.[8] Despite the versatility of the methyl-dithioester moiety, there are very few convenient procedures for its synthesis. Existing methods all require either the

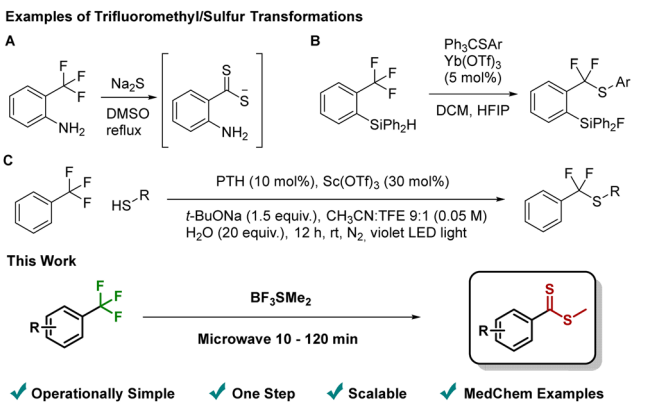

Fig. 1 Top: Examples of CF_3/sulfur transformations: (A) sulfur insertion into activated CF_3-group[3a]; (B) substrate assisted C–F activation[3b]; (C) Lewis acid promoted, photo-redox catalyzed C–F activation.[3c] Bottom: This work.

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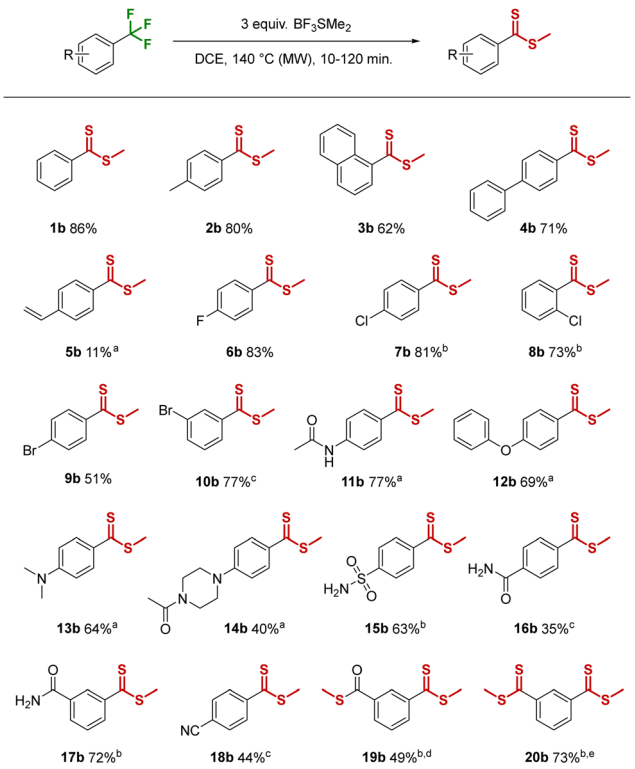
Table 1 Scope of the methyl-dithioester method



Isolated yields. Conditions unless otherwise specified: 0.5 mmol scale in 1 mL DCE at 140 °C (MW) for 30 min. [a] 10 min reaction time. [b] 60 min reaction time. [c] 120 min reaction time. [d] From 3-(trifluoromethyl)benzoic acid, 4 equiv. BF_3SMe_2 used. [e] 6 equiv. BF_3SMe_2 used.

use of complex[9] or expensive[10] reagents, sensitive organometallic precursors and toxic CS_2,[11] malodourous H_2S[12] or laborious multistep syntheses.[13] Therefore, the development of a novel, cheap and straightforward synthesis of this important functional group would be a valuable addition to the synthetic toolbox. Furthermore, a route from the relatively inert trifluoromethyl-moiety to the versatile dithioester-group would allow the selective downstream insertion of various functional groups in the late stages of a multistep synthesis.[14]

Herein we report the discovery and development of the first defluorinative synthesis of methyl-dithioesters from readily available trifluoromethyl arenes. Furthermore, this method was exemplified through the late-stage modification of drug molecules, highlighting its utility in real world applications.

Our initial investigation of the reaction conditions, using **1a** as model substrate, quickly revealed that elevated temperatures were advantageous, and heating at 120 °C for 1 h with 3 equivalents of BF_3SMe_2 afforded 74% of dithioester **1b** (Table S1, ESI†). A microwave reactor was employed to ensure rapid heating and pressure control, however conventional heating at lower temperature (80 °C) was also possible, but increased the reaction time significantly and resulted in lower yields. Screening different solvent conditions (neat, *i*-hexane, toluene) revealed DCE as the solvent of choice (83%), and a screen of temperature and time gave the optimal combination of 140 °C and 30 min. Finally, lowering the amount of Lewis acid (1.5 equiv. BF_3SMe_2 and 1.5 equiv. SMe_2) proved detrimental, resulting in incomplete conversion and only 30% isolated yield. With the optimized conditions in hand (3 equiv. BF_3SMe_2, DCE, 140 °C, 30 min) we proceeded to investigate the scope and functional group tolerance of the reaction (Table 1).

Toluene, naphthalene and 4-phenyl trifluoro substrates were well tolerated and produced methyl-dithioesters **2b**, **3b** and **4b** in 80%, 62% and 71% yield respectively. The presence of a 4-vinylbenzene group led to significant side-product formation/degradation, although with a 10 min reaction time the desired product **5b** could be isolated in 11% yield. 4-Fluoro and 4-chlorobenzotrifluoride were smoothly converted to the methyl-thioesters **6b** and **7b**, and a chloro-group in the *ortho*-position resulted in only a slight decrease in the yield of **8b**. 4-Bromobenzotrifluoride resulted in a moderate yield of **9b** (51%), due to competing thiomethyl substitution of the bromo group (**9b′**, 7% isolated yield, see Scheme S1, ESI†). However, no traces of bromo-substitution were observed using 3-bromobenzotrifluoride and the expected product **10b** was isolated in good yield (77%), although a longer reaction time (2 h) was required.

In contrast, the more electron-rich 4-(trifluoromethyl)acetanilide required only 10 min to reach full conversion, affording 77% of the desired product **11b**. The same trend was observed for 1-phenoxy-4-(trifluoromethyl)benzene and *N*,*N*-dimethyl-4-(trifluoromethyl)aniline affording 69% and 64% of **12b** and **13b** respectively after 10 min reaction time. A free NH-group in 1-(4-(trifluoromethyl)phenyl)piperazine was unfortunately not tolerated (see Scheme S2 for unsuccessful substrates, ESI†), resulting in an insoluble black solid. This could be overcome by acetyl-protection and the corresponding target acetamide product **14b** was isolated in 40% yield.

Turning to more electron-deficient substrates, 4-(trifluoromethyl)benzenesulfonamide gave the dithioester **15b** in a moderate yield of 63%. The reaction of 4-(trifluoromethyl)-benzamide was rather sluggish and led to a modest yield of **16b** (35%). However, moving the position of the electron withdrawing group with 3-(trifluoromethyl)benzamide changed the reactivity drastically, affording 72% of **17b** after 60 min. The presence of a strong electron withdrawing group in 4-(trifluoromethyl)benzonitrile afforded a moderate 44% yield of **18b** after 2 h of heating. Electron deficient heteroaromatic pyridines (2-(trifluoromethyl)- and 3-(trifluoromethyl)pyridine) were found to be completely inert under the reaction conditions, returning only unreacted starting material.

3-(Trifluoromethyl)benzoic acid, in addition to methyl-dithioester formation, also resulted in OH-substitution to form the thioester **19b** in 26% yield, which could be improved to 49% by increasing the amount of BF_3SMe_2. Finally, 1,3-bis(trifluoromethyl)benzene was also successfully converted into the 1,3-dithioester **20b** in good yield (73%).

Potential halide selectivity was explored by reacting 1-(trichloromethyl)-3-(trifluoromethyl)benzene under the conditions. Interestingly, both functional groups were transformed into methyl dithioesters and the 1,3-bis methyl dithioester **20b** was

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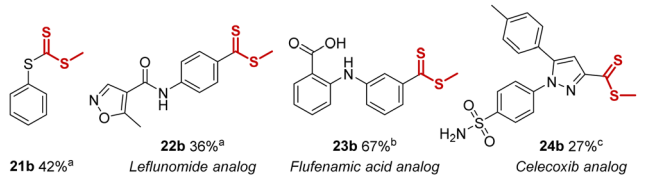
Table 2 Additional transformations and late-stage functionalization



Isolated yields. Conditions unless otherwise specified: 0.5mmol scale in 1 mL DCE at 140 °C (MW). [a] 10 min reaction time. [b] 80 °C for 18 h. [c] 120 min reaction time.

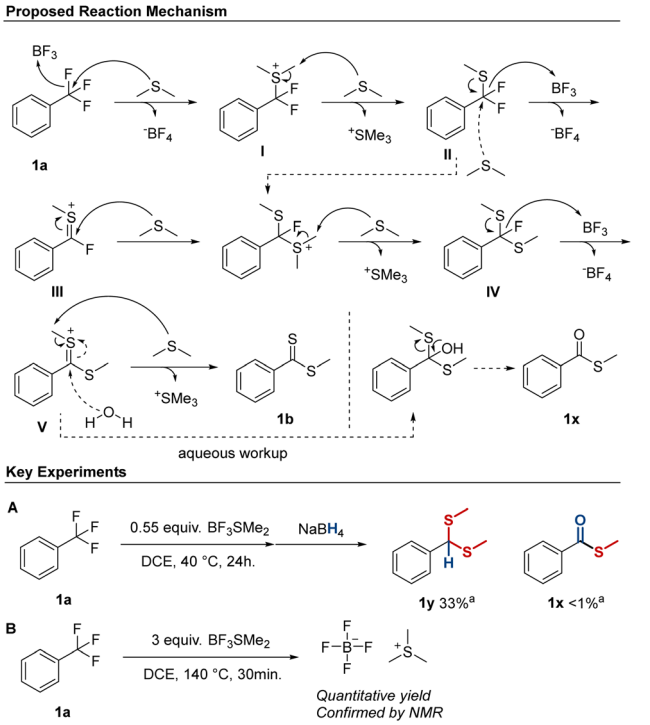
isolated in 82% yield. This demonstrates that the trichloromethyl moiety is also a viable substrate for direct methyl-dithioester synthesis.

The scalability of this method was also explored, and the conditions were applied on a 5 mmol scale using trifluorotoluene (**1a**). Pleasingly, no reduction in yield was observed with the methyl-dithioester **1b** isolated in 85% yield, highlighting the utility of this method on a preparative scale.

During our exploration of non-aromatic trifluoromethyl-groups, we found (trifluoromethoxy)benzene and (2,2,2-trifluoroethyl)benzene to be unsuitable for this method due to competing side-reactions (*e.g.* demethylation). In contrast, trifluoromethylthiobenzene was found to be a productive substrate, leading to formation of the rarely encountered trithiocarbonate functional group, and **21b** was isolated in 42% yield (Table 2). Notably, this is the first trithiocarbonate synthesis that does not require odorous sulfides or activated thiocarbonyl substrates. Furthermore, the method could also be applied to the late-stage functionalization of the antirheumatic drug leflunomide and the nonsteroidal anti-inflammatory drugs flufenamic acid and celecoxib. All three substrates were smoothly converted into novel methyl-dithioester analogs **22b**, **23b** and **24b** in useful yields of 36%, 67% and 27% respectively, representing interesting late-stage transformations (Table 2).

The mechanism of the defluorination/thioester synthesis is thought to proceed *via* an initial defluorination of the trifluoromethyl group by BF_3, followed by attack from SMe_2, resulting in intermediate **I** (Scheme 1). The higher reactivity of electron-rich substrates suggest that this occurs *via* an S_N1-type mechanism in accordance with other Lewis acid mediated defluorination processes.[15] Following this, demethylation of the thionium ion occurs to give **II**, followed by abstraction of a second fluorine, resulting in intermediate **III**. Intermediate **III** should be highly electrophilic, and react readily with a second SMe_2 molecule, which after demethylation results in the fluoro-thioacetal intermediate **IV**. Alternatively, intermediate **IV** can also be formed by an S_N2-type attack by SMe_2 on intermediate **II** followed by demethylation (Scheme 1, dotted line). Intermediate **IV** is then converted into **V** *via* a third defluorination and this is followed by a final demethylation to form the methyl-dithioester product, compound **1b**.

To further delineate the reaction mechanism a number of control experiments were performed (ESI,† Scheme S3). In an attempt to form intermediate **I**, **1a** was reacted with 0.55 equiv.



Scheme 1 Proposed mechanism for the transformation of the trifluoromethyl group into the methyl-dithioester using BF_3SMe_2 and key experiments supporting intermediate **V** (A), and SMe_2 as demethylating reagent (B). [a] Yields determined by ^{1}H-NMR.

of BF_3SMe_2 at 40 °C (ESI,† Experiment 1). This failed to produce intermediate **I**, and aqueous workup instead revealed *S*-methyl carbothioate (thioester) **1x** as the major product (22%, NMR) along with a minor amount of methyl-dithioacetal **1y** (9%). Thioester formation was also observed during the previous scope investigation of some trifluoromethyl substrates, and we had reasoned that the formation could be due to the presence of moisture in the reaction mixture.

To investigate this, a small amount of water (1.1 equiv.) was added to our standard conditions. This was surprisingly well-tolerated, and 64% of dithioester **1b** was formed. Notably, there were only traces of **1x** detected, indicating that water was not the main reason for thioester formation and we were therefore curious to further probe the origins of **1x**. The presence of thioacetal **1y** supported the formation of intermediate **V**, and we therefore treated the crude reaction mixture from experiment 1 with $NaBH_4$ instead of performing an aqueous work up (Scheme 1A). This resulted in formation of significant amounts of dithioacetal **1y**, and only traces of **1x** were detected. We therefore suggest that **1x** is formed from intermediate **V** during aqueous workup rather than during the reaction (Scheme 1).

Finally, we investigated our hypothesis of SMe_2 acting as the demethylating species, as there is also the possibility that the demethylation occurs *via* a halide (fluoro) nucleophile. This pathway was suggested by Ikeada *et al.*[16] using BBr_3 as C–F activator and methanol as nucleophile forming carbonyls from trifluoromethyl groups. By treating a crude reaction mixture with *i*-hexane, a residue was formed, which upon further

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purification resulted in an off-white solid (Scheme 1B). This was analyzed by NMR and the data were consistent with the formation of trimethyl sulfonium tetrafluoroborate (^{1}H-, ^{13}C- and ^{19}F NMR). This, together with the amount of trimethyl sulfonium tetrafluoroborate recovered (quant.), suggests that SMe_2 is the predominant demethylating reagent under these conditions, which is in line with the known demethylating properties of BF_3SMe_2.

In conclusion, we have developed a new strategy for the activation of the trifluoromethyl group and its transformation into methyl-dithioesters. The methyl-dithioester is a versatile and useful group in synthetic chemistry and this method offers not only a valuable alternative entry point but also arguably the most straight-forward route to this functional group. We have also reported a rare example of a trithiocarbonate synthesis, as well as applications on active pharmaceutical scaffolds. We hope that these efforts will encourage the further investigation into the application of this unusual synthetic handle, and applications of this method towards other transformations are currently underway in our laboratory.

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Data availability

Data for this article, including details on experimental procedures, mechanistic experiments and characterization data of all compounds are available as part of the ESI.†[17]

Conflicts of interest

There are no conflicts to declare.

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