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Late-stage defluorinative functionalization: synthesis of thio-amides and heterocycles from trifluoromethylarenes

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A novel transformation of trifluoromethyl arenes into thioamides has been developed. The reaction proceeds in a two-step, one-pot fashion *via* a methyl–dithioester intermediate formed in a defluorination/thiolation using $\text{BF}_3\cdot\text{SMe}_2$, followed by a mild and rapid substitution of the thiomethyl–moiety. The method was compatible with the synthesis of both secondary and tertiary thioamides, using a wide range of trifluoromethylarenes. In addition, the method was successfully extended to the synthesis of various heterocycles by utilizing amines with specific pendant functionalities. Finally, the method was demonstrated as a potent late-stage approach when applied to the installation of thioamides and heterocycles into flufenamic acid, cinacalcet, leflunomide and celecoxib as well as amino acid/peptide modifications.

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Introduction

The trifluoromethyl (CF_3) group is a common motif in many biologically active molecules, where it influences structural, electronic and biological properties, making it highly prevalent in pharmaceuticals.¹ In addition, the CF_3 -group has also received substantial recent interest as a synthetic handle.^{2–8} The inertness and high activation energy of the C–F bond pose a significant challenge for chemists in the development of new methods to unlock its synthetic potential. On the other hand, the stability of the CF_3 group offers an opportunity for its early incorporation into synthetic pathways, enabling selective chemical transformations later in the sequence or as a final step.⁹

We have recently reported a novel approach for the transformation of trifluoromethylarenes into methyl–dithioesters using the commercially available reagent $\text{BF}_3\cdot\text{SMe}_2$ as a dual-purpose defluorinative (*via* BF_3) and thiolating (*via* SMe_2) reagent.¹⁰

In our exploration of the reaction mechanism, we discovered that the main by-products from the reaction was the relatively inert $\text{BF}_4^+\text{SMe}_3^-$ salt. As such, the combination of a reactive dithioester functional group and non-interfering by-products, would lend itself to an extension of the methodology *via* a one-pot synthesis of other functional groups, enabling further exploration of novel trifluoromethyl transformations. A one-pot procedure also provides a powerful and efficient strategy for late-stage functionalization of the relatively inert tri-

fluoromethyl group, enabling rapid access to thioamide derivatives while eliminating the need to isolate and handle unstable dithioester intermediates.

The thioamide group is an important functional group due to its impact on medicinal chemistry,¹¹ occurrence in various biologically active natural products¹² (such as cycasthioamide,¹³ thioviridamide,¹⁴ and closthioamide¹⁵) and use in peptide modifications.¹⁶ The thioamide moiety can, for example, be seen in ethionamide, an antibiotic used against tuberculosis, mercaptopurine, used for cancer and autoimmune disease treatment, elesclomol, a cancer cell apoptosis inducer, and fimasartan, an angiotensin II receptor antagonist (Fig. 1). Furthermore it has been shown that an amide to thioamide substitution in peptides can improve stability against proteolysis¹⁷ improve permeability¹⁸ and influence hydrogen-bonding in peptides,¹⁹ among other beneficial effects.¹⁶

The functional group has also found significant utility as a synthetic intermediate, especially as a heterocycle precursor.²⁰ The combination of nitrogen and sulfur nucleophilicity, the electrophilic thiocarbonyl carbon, the delocalized π -system, and the leaving group potential of the thiocarbonyl sulfur lend the thioamide group to numerous synthetic possibilities. The importance of the thioamide moiety is further highlighted by the numerous reported methods for its synthesis. From classical examples such as the Willgerdt–Kindler reaction²¹ using ketones or aldehydes, and the thionylation of amides using Lawesson's²² or related reagents, to current literature that now offers diverse examples and strategies for synthesizing thioamides from a variety of functional groups.^{16,23}

Despite this, to the best of our knowledge, a trifluoromethyl to thioamide conversion has never been reported. Such a trans-

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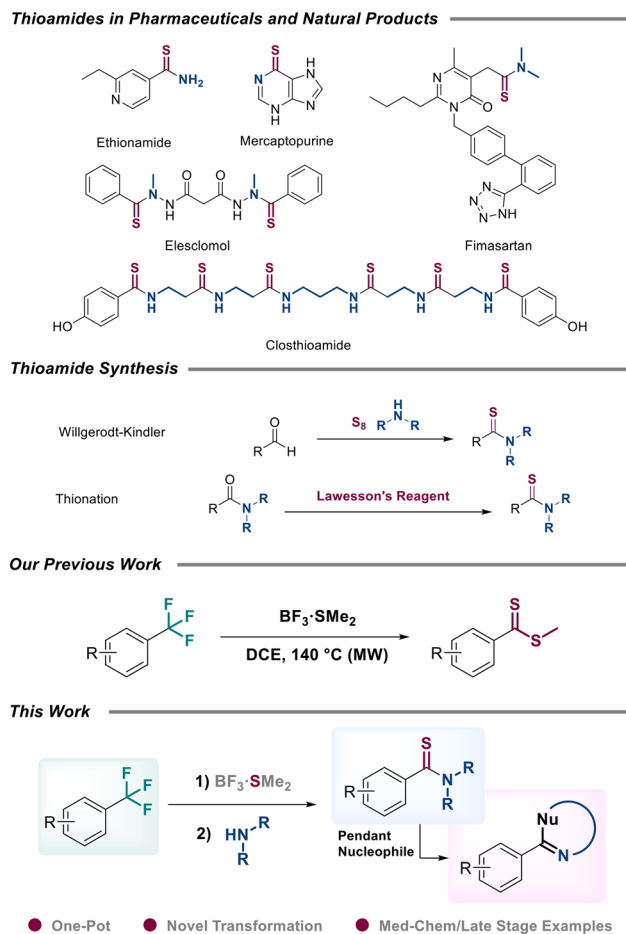


Fig. 1 The thioamide in biologically relevant molecules, classic dithioester synthesis, our previous work, and this work.

formation would unlock useful late-stage opportunities for the insertion of a thioamide group, following incorporation of the stable trifluoromethyl group early in a synthetic route. This in combination with the versatility of the thioamide moiety for further introduction of more complex structures would provide a powerful tool in medicinal chemistry synthesis efforts. We therefore aimed to develop the first strategy for the conversion of trifluoromethylarenes into thioamides *via* a telescoped two-step dithioester/amine substitution approach.

Herein we report a method for the transformation of trifluoromethylarenes into thioamides. In addition, we also report the further transformation of thioamides into various heterocyclic moieties, representing the first generally applicable trifluoromethyl to heterocycle conversion. Finally, we demonstrate the utility of the method by applying it to approved pharmaceuticals and amino acids, highlighting its use in real world applications.

Results and discussion

We began our investigation using trifluorotoluene (**1a**) as the substrate and piperidine as our model nucleophile, opting for

direct addition of the amine to the crude methyl-dithioester reaction mixture in a one-pot approach. Addition of 2 equiv. of piperidine and stirring at room temperature resulted in only trace amounts of the thioamide product **1b**, even after a 24 h reaction time (Table 1, entry 1).

However, when the amount of piperidine was increased to 4 equivalents the desired thioamide **1b** could be isolated in 79% yield, although complete conversion of methyl-dithioester was not achieved (entry 2). When increasing to 6 equiv. the transformation proceeded to full conversion within 60 min and the thioamide product was isolated in 86% yield (entry 3). We suspect that any leftover acid from the first step renders the amine unreactive, therefore necessitating the addition of excess base/nucleophile.

As the amount of amine could be a potential problem using high-molecular weight or precious nucleophiles, we explored the addition of an alternative base for neutralization. This proved effective, as the addition of Et_3N prior to the nucleophile yielded comparable results, requiring only 2 equivalents of piperidine (entry 4). Starting from the isolated methyl-dithioester (entry 5) gave a slightly higher yield, but overall affords a lower yield calculated over two-steps from trifluorotoluene, highlighting the advantage of a one-pot procedure.

With these conditions in hand, we proceeded to investigate various amine nucleophiles (Table 2). Primary amines were found to be suitable substrates, affording thioamides **2b-8b** in 47–86% yield. Notably, this included **2b** where methylamine was added in an ethanol solution, demonstrating excellent chemoselectivity. This was also observed when using ethanolamine as a nucleophile, resulting in exclusive formation of thioamide **6b**. It was also possible to use ethylenediamine as the nucleophile without excessive dimerization, although the product was isolated as its *N*-acetylated analogue **7b** to facilitate purification. In addition, pre-treating the reaction with Et_3N to reduce the amount of nucleophile needed was again demonstrated with 2-picolylamine, where the product **8b** was isolated in 82% yield. Using primary amines generally resulted

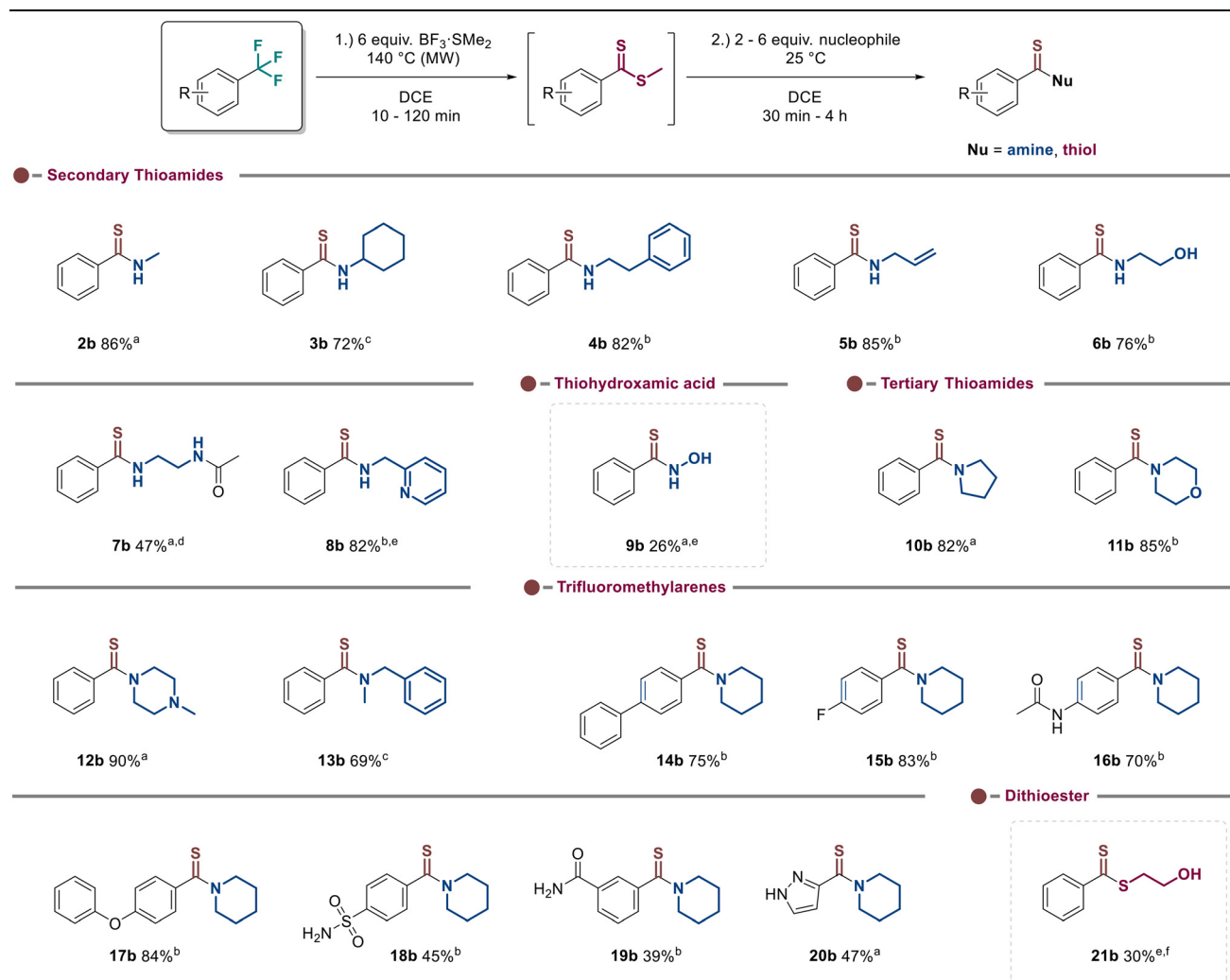
Table 1 Exploration of the one pot synthesis of thioamides from trifluoromethylarenes

Entry	Piperidine (equiv.)	Time	Yield ^a
1	2	24 h	Trace
2	4	4 h	79%
3	6	1 h	86%
4	2 ^b	1 h	86%
5 ^c	6	30 min	90% (78%) ^d

Conditions: 0.5 mmol scale in 1 mL DCE. ^a Isolated yield. ^b 4 equiv. Et_3N added before piperidine. ^c Starting from isolated methyl-dithioester. ^d Yield calculated over two steps starting from **1a**.



Table 2 Scope of the one-pot synthesis of thioamides from aryltrifluoromethanes



Isolated yields. Conditions unless otherwise stated: 0.5 mmol scale in 1 mL DCE. Time for step 1 according to previous publication:¹⁰ **2a-15b**, **21b** 30 min. **16b-17b** 10 min. **18b-19b** 60 min. **20b** 120 min. Time for step 2. ^a 30 min. ^b 60 min. ^c 4 h. ^d 10 equiv. acetic anhydride was added after step 2. ^e Pre-treated with 4–6 equiv. Et₃N before adding 2 equiv. nucleophile in step 2. ^f 6 h under N₂ stream.

in complete conversion of the dithioester within 60 minutes, although with a more sterically hindered nucleophile in cyclohexaneamine, the reaction required 4 h to achieve complete conversion to thioamide **3b**.

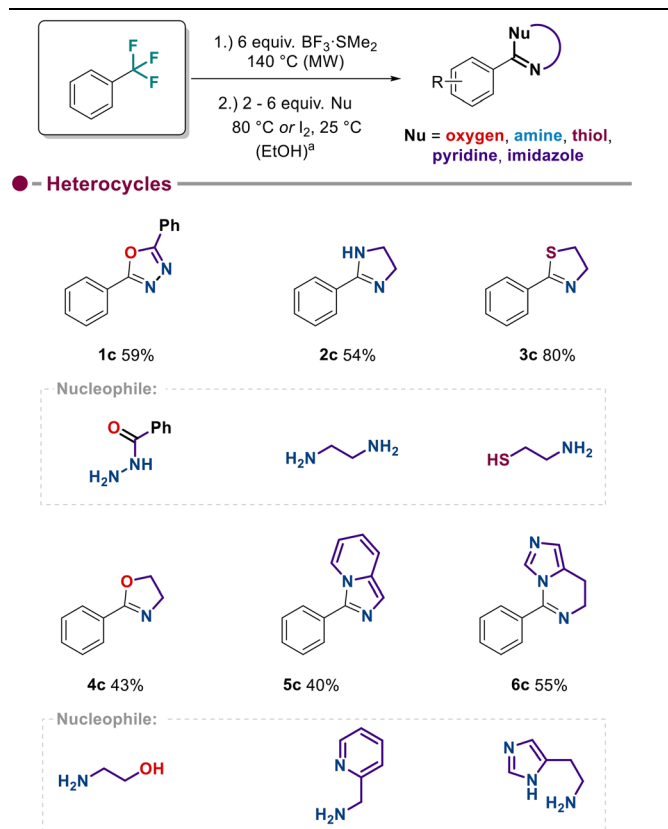
Of note is that the unusual thiohydroxamic acid functional group in **9b** could also be achieved with this method, requiring fewer steps compared to recently developed methods.²⁴

Cyclic secondary amines pyrrolidine, morpholine and *N*-methylpiperazine were all smoothly converted to the corresponding thioamides **10b-12b** in good yields. *N*-Methylated amines were also viable substrates and the reaction with *N*-methylbenzylamine led to a 69% isolated yield of **13b** after a 4 h reaction time. Unfortunately, reaction with poorer nucleophiles such as anilines and ammonia led to only traces of the desired products (Fig. S2).

Next, the trifluoromethylarene scope was also examined and a phenyl, fluoro, acetamide and a phenoxy group were all well-

tolerated returning isolated yields of 70–84% (**14b-17b**). The electron-poor substrates 3-(trifluoromethyl)benzamide and 4-(trifluoromethyl)benzenesulfonamide were also converted into the corresponding thioamides **18b** and **19b** in moderate yields of 45% and 39%, respectively. These yields are in line with those previously reported for dithioester synthesis.¹⁰ Finally, 3-(trifluoromethyl)-1*H*-pyrazole could be converted to the thioamide **20b** using this strategy. Notably, the methyl-dithioester intermediate had been previously observed, but could not be isolated due to stability issues. The thioamide was however stable towards purification and was easily isolated in 47% yield. Scaling up the reaction was also possible, and a 5 mmol reaction with piperidine resulted in 87% yield of thioamide **1b**. Aliphatic trifluoromethyl substrates were not suitable for this method, as no intermediate was seen in the dithioester forming step, presumably due to low stabilization of the proposed carbocation intermediate¹⁰ during defluorination.



Table 3 Scope of the trifluoro group to heterocycle transformation

Isolated yields. Heating (80 °C, **1c**, **2c**, **3c**) or I_2 (**4c**, **5c**, **6c**) used to facilitate cyclization. If insoluble. ^aEtOH was added as co-solvent (**1c**, **3c**, **5c**, **6c**). Reactions using larger nucleophiles (**1c**, **5c**, **6c**) were pre-treated with 4–8 equiv. Et_3N (depending on if nucleophile was HCl salt or not), followed by 2 equiv. nucleophile. See SI for detailed information.

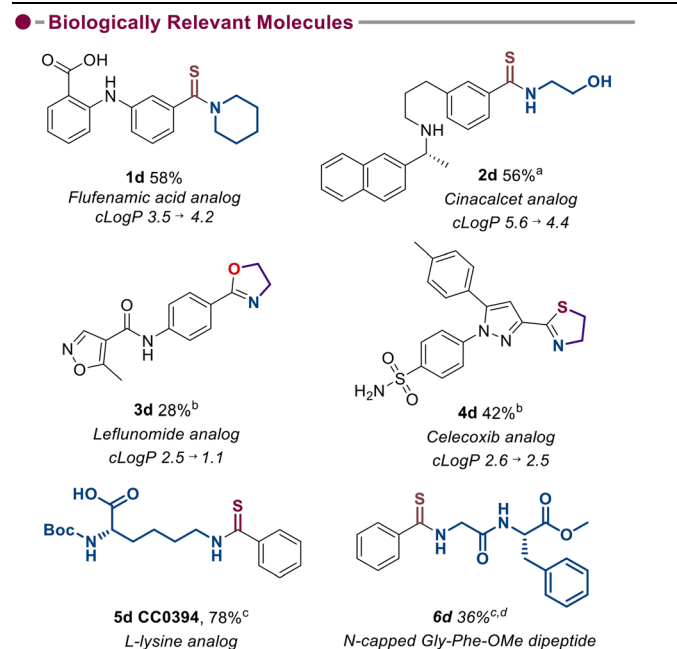
We also wanted to explore the possibility of varying the dithioester moiety using thiol nucleophiles. Quenching the reaction with Et_3N , followed by addition of 2-mercaptoethanol resulted in product formation (LCMS analysis), however full conversion of the dithioester intermediate could not be achieved, even after an extended reaction time. Increasing the amount of nucleophile improved conversion slightly, and a large excess (>10 equiv.) of thiol led to significant side-product formation. We suspected that the low conversion was a result of reversible addition of 2-mercaptoethanol and methanethiol. Therefore, a reaction was run under a gentle stream of nitrogen to remove gaseous methanethiol from the reaction mixture. This resulted in complete consumption of the intermediate and the desired dithioester **21b** was isolated in a 30% yield.

To further demonstrate the versatility of the trifluoromethylarene as a synthetic handle, we sought to develop a CF_3 to heterocycle interconversion (Table 3). Importantly, this would represent a powerful new tool for medicinal chemists to fundamentally alter compound properties during optimization campaigns. To this end, we first examined the addition of

benzhydrazide, which upon heating at 80 °C overnight, afforded the oxadiazole **1c** in 59% yield. This transformation is thought to proceed *via* initial formation of a thiohydrazide, followed by a subsequent attack from the carbonyl oxygen at the thiocarbonyl center followed by desulfurization and aromatization. Indeed, similar transformations from the thioamide have been reported before, although these utilize hypervalent iodine species to induce cyclization.²⁵ This methodology was extended to other di-nucleophiles (ethylenediamine and cysteamine), and led to the successful synthesis of imidazoline **2c** and thioazoline **3c** in useful yields.

In contrast, the less reactive nucleophiles ethanolamine, 2-picolylamine and histamine did not undergo cyclization under heating conditions and returned only the corresponding thioamide products. Therefore, I_2 activation of the thiocarbonyl²⁶ was employed to facilitate the heterocyclization. Using this modification, oxazoline **4c**, imidazo[1,5- α]pyridine **5c** and 7,8-dihydroimidazo[1,5- c]pyrimidine **6c** were all successfully synthesized from trifluorotoluene in 40–55% yield.

This is, to the best of our knowledge, the first generally applicable synthesis of heterocycles from a non-activated trifluoromethyl group,^{27–31} and the first report of the dihydro version of the imidazo[1,5- c]pyrimidine ring system. This clearly illustrates the potential of our method in achieving

Table 4 Applications of developed methods towards biologically relevant molecules

Isolated yields. Following general procedures described above. ^a10 equiv. nucleophile used. ^b I_2 (**3d**) or Heating (80 °C, **4d**) used to facilitate cyclization. ^cYields calculated from amino acid/peptide as limiting reagents (0.25 mmol) using excess trifluorotoluene (0.5 mmol). ^dThe Fmoc protected peptide was first deprotected *in situ* (see SI for details) before being added to the reaction mixture. If the mixture was insoluble, EtOH or MeOH was added as co-solvent. See SI for detailed information.



unique functional group transformations. It is also of note that no signs of aromatization of **2c-4c** and **6c** could be observed under these conditions.

Next, to probe the potential for late-stage modifications in medicinal chemistry, we applied these methodologies towards pharmaceutically and biologically relevant molecules (Table 4). Flufenamic acid could be converted to the piperidine thioamide **1d** in 58% yield. Here the first step of the reaction was performed at 80 °C overnight, to minimize side-reactions. Cinacalcet could be transformed into the more hydrophilic ethanol-thioamide **2d** in 56% yield. It is notable that an aliphatic amine was well-tolerated and the compound also retained optical activity, indicating minimal epimerization at the naphthylamine centre. For heterocyclic transformations, leflunomide was converted into the oxazoline analog **3d** in 28% yield, while celecoxib was decorated with a thiazoline motif (**4d**) in 42% yield. Notably the yield for **4d** was improved compared to isolation of the unstable dithioester analog,¹⁰ highlighting the advantage of thioamide formation in a one-pot procedure.

Finally, as the thioamide moiety can have profound influence on the chemical and biological properties of peptides,¹⁶ we also wanted to explore its installation onto amino acids. Accordingly, we thioacylated a Boc-protected lysine, affording the novel unnatural amino acid **5d** in 78% yield, as well as thioacylated the *N*-terminal of dipeptide Gly-Phe-OME affording **6d** in 36% yield.

Conclusions

In conclusion, we have developed a one-pot strategy for the synthesis of biologically and synthetically important thioamides from trifluoromethylarenes, enabling powerful new retrosynthetic disconnections. We have also demonstrated the utility of this approach towards more complex transformations, including the successful incorporation of diverse heterocyclic moieties. In addition, these methods have been successfully applied to the late-stage functionalization of pharmaceuticals, leading to novel analogs with significantly altered physicochemical properties. We hope these findings will prove valuable in future synthetic and drug discovery efforts.

Author contributions

MS and LO: conceptualization of the project. MS: design and development of the synthetic method. MS and EOH: synthesis and reaction scope. LO: project supervision. MS: first manuscript draft. MS, EOH and LO: review and editing of manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information is available. See DOI: <https://doi.org/10.1039/d5qo01574j>.

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References

- 1 A. S. Nair, A. K. Singh, A. Kumar, S. Kumar, S. Sukumaran, V. P. Koyiparambath, L. K. Pappachen, T. M. Rangarajan, H. Kim and B. Mathew, FDA-Approved Trifluoromethyl Group-Containing Drugs: A Review of 20 Years, *Processes*, 2022, **10**, 2054.
- 2 H. Amii and K. Uneyama, C–F Bond Activation in Organic Synthesis, *Chem. Rev.*, 2009, **109**, 2119–2183.
- 3 T. Stahl, H. F. T. Klare and M. Oestreich, Main-Group Lewis Acids for C–F Bond Activation, *ACS Catal.*, 2013, **3**, 1578–1587.
- 4 T. Fujita, K. Fuchibe and J. Ichikawa, Transition–Metal–Mediated and–Catalyzed C–F Bond Activation by Fluorine Elimination, *Angew. Chem., Int. Ed.*, 2019, **58**, 390–402.
- 5 X. Ma and Q. Song, Recent Progress on Selective Deconstructive Modes of Halodifluoromethyl and Trifluoromethyl-Containing Reagents, *Chem. Soc. Rev.*, 2020, **49**, 9197–9219.
- 6 G. Yan, K. Qiu and M. Guo, Recent Advance in the C–F Bond Functionalization of Trifluoromethyl-Containing Compounds, *Org. Chem. Front.*, 2021, **8**, 3915–3942.
- 7 Z. Wang, Y. Sun, L. Y. Shen, W. C. Yang, F. Meng and P. Li, Photochemical and Electrochemical Strategies in C–F Bond Activation and Functionalization, *Org. Chem. Front.*, 2022, **9**, 853–873.
- 8 K. Lye and R. D. Young, A Review of Frustrated Lewis Pair Enabled Monoselective C–F Bond Activation, *Chem. Sci.*, 2024, **15**, 2712–2724.
- 9 L. V. Hooker and J. S. Bandar, Synthetic Advantages of Defluorinative C–F Bond Functionalization, *Angew. Chem., Int. Ed.*, 2023, **62**, e202308880.
- 10 M. Söderström, E. Olaniran Håkansson and L. R. Odell, Defluorinative Thio-Functionalization: Direct Synthesis of Methyl-Dithioesters from Trifluoromethylarenes, *Chem. Commun.*, 2025, **61**, 145–148.



- 11 G. Huang, T. Cierpicki and J. Grembecka, Thioamides in Medicinal Chemistry and as Small Molecule Therapeutic Agents, *Eur. J. Med. Chem.*, 2024, **277**, 116732.
- 12 N. Mahanta, D. M. Szantai-Kis, E. J. Petersson and D. A. Mitchell, Biosynthesis and Chemical Applications of Thioamides, *ACS Chem. Biol.*, 2019, **14**, 142–163.
- 13 M. Pan, T. J. Mabry, J. M. Beale and B. M. Mamiya, Nonprotein Amino Acids from *Cycas Revoluta*, *Phytochemistry*, 1997, **45**, 517–519.
- 14 Y. Hayakawa, K. Sasaki, H. Adachi, K. Furihata, K. Nagai and K. Shin-ya, Thioviridamide, a Novel Apoptosis Inducer in Transformed Cells from *Streptomyces Olivoviridis*, *J. Antibiot.*, 2006, **59**, 1–5.
- 15 T. Lincke, S. Behnken, K. Ishida, M. Roth and C. Hertweck, Closthioamide: An Unprecedented Polythioamide Antibiotic from the Strictly Anaerobic Bacterium *Clostridium cellulolyticum*, *Angew. Chem., Int. Ed.*, 2010, **49**, 2011–2013.
- 16 T. N. Hansen and C. A. Olsen, Contemporary Applications of Thioamides and Methods for their Synthesis, *Chem. – Eur. J.*, 2024, **30**, e202303770.
- 17 H. A. T. Phan, S. G. Giannakoulis, T. M. Barrett, C. Liu and E. J. Petersson, Rational Design of Thioamide Peptides as Selective Inhibitors of Cysteine Protease Cathepsin L, *Chem. Sci.*, 2021, **12**, 10825–10835.
- 18 P. Ghosh, N. Raj, H. Verma, M. Patel, S. Chakraborti, B. Khatri, C. M. Doreswamy, S. R. Anandakumar, S. Seekallu, M. B. Dinesh, G. Jadhav, P. N. Yadav and J. Chatterjee, An Amide to Thioamide Substitution Improves the Permeability and Bioavailability of Macrocyclic Peptides, *Nat. Commun.*, 2023, **14**, 6050.
- 19 H. Zheng and R. W. Newberry, Thioamides in C5 Hydrogen Bonds: Implications for Protein β -Strands, *J. Org. Chem.*, 2025, **90**, 13984–13988.
- 20 T. S. Jagodziński, Thioamides as Useful Synthons in the Synthesis of Heterocycles, *Chem. Rev.*, 2003, **103**, 197–228.
- 21 D. L. Priebsenow and C. Bolm, Recent Advances in the Willgerodt–Kindler Reaction, *Chem. Soc. Rev.*, 2013, **42**, 7870.
- 22 T. Ozturk, E. Ertas and O. Mert, Use of Lawesson's Reagent in Organic Syntheses, *Chem. Rev.*, 2007, **107**, 5210–5278.
- 23 Review: (a) Q. Zhang, L. Soulère and Y. Queneau, Towards More Practical Methods for the Chemical Synthesis of Thioamides using Sulfuration Agents: A Decade Update, *Molecules*, 2023, **28**, 3527; For some recent and relevant methods: (b) Y. Mumtaz, H. Xiang, J. Khan, S. Liang and W. Yi, One-Pot Synthesis of Thioamides via Nickel-Catalyzed Coupling of Thiocarbonyl Fluorides and Boronic Acids, *Eur. J. Org. Chem.*, 2024, e202400742; (c) Y. Li, H. Z. Tariq, S. Xu and J. Li, Chemoselective Thioamidation of Potassium Acyltrifluoroborates (KATs) and Amines Using Elemental Sulfur in Aqueous Solution, *Eur. J. Org. Chem.*, 2025, e202500330; (d) J. Gao, T. Wang, P. Li, Y. Luo, L. Fang, H. Zhai, J. Wang and B. Cheng, Visible-Light-Promoted Willgerodt–Kindler-Type Thioamidation Reaction of Amines, α -Ketoacids and Elemental Sulfur, *Eur. J. Org. Chem.*, 2025, e202500708; (e) J. Wu, Y. Liao, M. Pan, T. Song, J. Zhang, L. Li, J. Lu and X. Jiang, Synthesis of alkyl thioamides by three-component reactions of allyl alcohols, elemental sulfur and amines: elemental sulfur as a mild oxidant and a sulfur source, *Green Chem.*, 2025, **27**, 12160–12165; (f) V. Pace, L. Castoldi, S. Monticelli, S. Safranek, A. Roller, T. Langer and W. Holzer, A Robust, Eco-Friendly Access to Secondary Thioamides through the Addition of Organolithium Reagents to Isothiocyanates in Cyclopentyl Methyl Ether (CPME), *Chem. – Eur. J.*, 2015, **21**, 18966–18970.
- 24 B. C. Lemercier and J. G. Pierce, Synthesis of Thiohydroxamic acids and Thiohydroxamic Acid Derivatives, *J. Org. Chem.*, 2014, **79**, 2321–2330.
- 25 P. S. Chaudhari, S. P. Pathare and K. G. Akamanchi, *o*-Iodoxybenzoic Acid Mediated Oxidative Desulfurization Initiated Domino Reactions for Synthesis of Azoles, *J. Org. Chem.*, 2012, **77**, 3716–3723.
- 26 F. Shibahara, A. Kitagawa, E. Yamaguchi and T. Murai, Synthesis of 2-Azaindolizines by Using an Iodine-Mediated Oxidative Desulfurization Promoted Cyclization of *N*-2-Pyridylmethyl Thioamides and an Investigation of Their Photophysical Properties, *Org. Lett.*, 2006, **8**, 5621–5624.
- 27 Y. H. So and R. Decaire, 2-Arylbenzothiazoles and 2-Arylbenzoxazoles from α,α,α -Trihalomethyl Aromatic Compounds, *Synth. Commun.*, 1998, **28**, 4123–4135.
- 28 R. L. Wydra, S. E. Patterson and L. Streckowski, An Activated Trifluoromethyl Group as a New Synthon for 4,5-dihydro-1*H*-Imidazole and 1,4,5,6-tetrahydropyrimidine Systems, *J. Heterocycl. Chem.*, 1990, **27**, 803–805.
- 29 A. S. Kiselyov, M. Hojjat, K. Van Aken and L. Streckowski, An Activated Trifluoromethyl Group as a Synthon for 2-Substituted Benzothiazole and Benzoxazole, *Heterocycles*, 1994, **37**, 775.
- 30 J. X. Qiao, T. C. Wang, C. Hu, J. Li, R. R. Wexler and P. Y. S. Lam, Transformation of Anionically Activated Trifluoromethyl Groups to Heterocycles under Mild Aqueous Conditions, *Org. Lett.*, 2011, **13**, 1804–1807.
- 31 Q. Zou, Q. Meng, J. Wang and F. Li, Anion-Driven CF Bond Cleavage of Trifluoromethyl *N*-Aryl Hydrazones Toward the Assembly of *N*-Heterocycles, *Tetrahedron Lett.*, 2024, **151**, 155328.

