Shelf-Stable Electrophilic Reagents for the Direct Incorporation of SCF₂CF₂H and SCF₂CF₃ Motifs

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Abstract

The introduction of fluoroalkylthioether groups has attracted the attention of the drug discovery community given the special physicochemical and pharmacokinetic features they confer to bioactive compounds. Synthetic advances in the field have been capitalized by methods to incorporate SCF₃ and SCF₂H motifs, however, longer and synthetically more challenging polyfluoroethyl chains are still underdeveloped. Here, two saccharin-based electrophilic reagents have been disclosed for the efficient incorporation of SCF₂CF₂H and SCF₂CF₃ motifs. Their reactivity performance has been thoroughly investigated with a variety of nucleophiles such as thiols, alcohols, amines, alkenes, (hetero)aromatics, and organometallic species, including natural products and pharmaceuticals. Finally, multigram-scale preparation and divergent derivatization has been explored from SCF₂CF₂H derivatives.

Introduction

The introduction of fluoroalkyl motifs has been a cornerstone in synthetic, medicinal, and crop chemistry by virtue of the fine-tuning optimization of physicochemical properties of the modified compounds.¹ Over the last few years, the so-called fluorinated emerging motifs² have entered this arena to find structural alternatives to the most exploited CF₃ and F substituents. In this immense scenario, thiofluoroalkyl motifs (SRᵣ) occupy a privileged position since the association of fluoroalkyl chains with sulfur results in a powerful combination.³ The high electronegativity induced by the fluorine atoms combined with the electronic density of the chalcogen, renders highly lipophilic fragments.⁴ In medicinal chemistry, these attributes are interesting as they lead to more metabolically stable and higher cell-membrane/blood-brain-barrier permeable ingredients, thus, increasing the bioavailability of drug candidates.⁵ Fluoroalkyl modified thioethers not only show outstanding Hansch lipophilicity (e.g. CF₃, 0.88 vs. SCF₃, 1.44)⁶ but also serve as pivotal groups to access other appreciated derivatives, including fluorinated sulfones, sulfonamides, and sulfoximines.⁷ Collectively, these groups exhibit unique properties and represent new avenues for the development of improved bioactive compounds (Fig. 1A). Classically, SRᵣ motifs have been prepared by fluoroalkylation of SH, S₂, SCI, or SCN moieties via S–Rᵣ disconnection (Fig. 1B, right panel).⁸
Fig. 1 Selected drugs containing SCF₃ and SCF₂H groups and the homologation equivalent SCF₂CF₂H (panel A). Synthetic strategy and disconnections to R–SRᵣ motifs (panel B). Reports on the installation of selected SRᵣ motifs and MedChem targets containing these fragments. Biophysical significance of SCF₂CF₃ and SCF₂CF₂H motifs (panel C). Hits obtained with Reaxys database. For Van der Waals (VdW) volume calculation see ref. 9. For electrostatic potential surface calculation see ref. 10.

However, this strategy is not amenable to late-stage functionalization as it requires a preinstalled sulfur handle in the parent molecule. For this reason, fluoroalkylthiolating reagents (and other direct, one-pot protocols) have emerged as a power alternative for the direct modification of target compounds via C–S disconnection (Fig. 1B, left panel). In recent years, most of the vast number of reports describing nucleophilic, electrophilic, radical, or oxidative fluoroalkylthiolating agents/protocols are limited to the introduction of SCF₃, followed in number by SCF₂H. Despite recent advances in the field, drug development comprising other polyfluorinated ethyl congeners is virtually absent (Fig. 1C, right panel). Compared to the SCF₃ motif, SCF₂CF₂H and SCF₂CF₃ fragments confer a larger Van der Waals volume (81.7 Å³ and 87.7 Å³, respectively vs. 58.3 Å³ for SCF₃). Thus, higher lipophilicity is expected because of the increase in fluorination degree, although subtle differences in polarity may arise due to the uncommon fluorination patterns (Fig. 1C, right panel). Alike the CF₂H group, examination of the electrostatic potential surface of PhSCF₂CF₂H indicates a terminal electropositive region, suggesting the capability of this group to act as a hydrogen bond donor (Figs. S5 and S6, ESI†). Besides a few one-pot nucleophilic/radical methods, to the best of our knowledge, only two N-electrophilic sulfenamide reagents have been disclosed by Billard for the introduction of the SCF₂CF₃ motif. However, the electrophilic reactivity shown is limited to the modification of two examples of activated aromatics (phenol and 1,3-dimethoxybenzene), ethyl lithium, and Grignard nucleophiles. On the other hand, although mechanistically different to the prototypical N-electrophilic reagents, the in situ generated “SCF₂F₃ anion from either sulfenamide reagents by Billard” or from benzothiazolium reagents by Hopkinson.
enabled the formal incorporation of the SCF₂CF₃ motif via nucleophilic substitution of halides, tosylates/mesylates, or alcohols, respectively. Concerning the other potentially valuable SCF₂CF₂H fragment, and although recent efforts have been undertaken towards the development of tetrafluoroethylation protocols²¹,²² direct transfer of tetrafluoroethythioether units still remains uncharted.

Results and discussion

Reagent Design and Development

Willing to develop electrophilic reagents able to transfer the aforementioned thiofluoroalkyl chains, we turned our attention to imide and sulfonamide-based scaffolds. Typically, the N–S–R₆ triad in these reagents is constructed by a general nucleophilic approach from either thiolate salts and N-Cl compounds (for SCF₃)²³ or AgCF₂H and N-SCI precursors (for SCF₂H).¹³ However, longer fluoroalkyl thiols show very low stability due to α-fluoride elimination processes.²⁴ Thus, all our first attempts using the *in situ* generated M⁺–SC₂F₅, (M⁺ = Ag⁺, Cu⁺, NMe₄⁺)²⁵ were unsuccessful (Fig. 2A). In view of these results, we decided to adjust the synthetic strategy using electrophilic +SRF synthons for the preparation of the final electrophilic reagents (Fig. 2B).²⁶ Thus, chlorination of readily available 1,1,2,2-tetrafluoroethyl 1a and pentafluoroethyl 1b benzyl thioethers gave access to key sulfenyl chlorides,²⁷ which reacted with various imide, and sulfonamide salts to render a family of N-reagents 2a–8a, 8b, featuring succinimide, phthalimide, saccharine, and sulfonamides as representative leaving groups. Importantly, this synthetic protocol uses cheap and widely available starting materials, making it suitable for scaling-up reactions (up to 52 g of 8a prepared). The choice of the optimal reagent was based on a balance between synthetic yield, reactivity, stability, and cost (Table S1, ESI†). Saccharine-SCF₂CF₂H 8a and SCF₂CF₃ 8b exhibited the best overall results (Fig. 2C).⁹
A. Preliminary studies: nucleophilic strategy

\[ \text{S}8 + \text{TMSCF}_2\text{CF}_3 \rightarrow \text{SCF}_2\text{CF}_3 \text{Cl} \]

(a) CsF, THF. (b) MeNF, monoglyme or diglyme or THF. (c) KF, CuBr or CuI, DMF. (d) AgF, DMF.

B. Reagent synthesis: electrophilic strategy

\[ \text{SCF}_2\text{CF}_3 \text{H} + \text{TMS} \rightarrow \text{SCF}_2\text{CF}_3 \]

Ex situ gas generation

Multigram scale

No special equipment required

Allows for different leaving group installation (R^1R^2N)

C. Reagent optimization

Leaving group choice

Best reactivity/stability balance

Ready available & cheap precursors

No chromatography required

Fig. 2 Preliminary attempts for the preparation of SCF$_2$CF$_3$ reagent 3b using the standard nucleophilic route (panel A). Umpolung (electrophilic) route to SCF$_2$CF$_2$H 2a–8a and SCF$_2$CF$_3$ 8b reagents (panel B). Reagent optimization (panel C). See the ESI$^+$ for details. TMS = trimethylsilyl, TCCA = trichloroisocyanuric acid.
Scheme 1 Scope of nucleophiles (panel A) and functionalization of natural products and pharmaceuticals (panel B). Reagents and conditions: (a) 1H-indole (1.0 equiv), CH$_2$Cl$_2$, 40 ºC. (b) PhOH (1.0 equiv), 8a,b (1.2 equiv), TFOH (1.0 equiv), CH$_2$Cl$_2$, rt. (c) BnNH$_2$ (1.0 equiv), 8a,b (1.1 equiv), CH$_2$Cl$_2$, rt. (d) 2-Mercaptobenzoxazole (1.0 equiv), 8a,b (1.1 equiv), CH$_2$Cl$_2$, rt. (e) Adamantol (1.0 equiv), 8a,b (1.3 equiv), Et$_3$N (2.5 equiv), CH$_2$Cl$_2$, rt. (f) (i) 2,2-Dimethylcyclopentan-1-one (1.0 equiv), KHMDS (1.2), (ii) 8a,b (2.5 equiv), THF, –78 ºC. (g) (i) Diethyl 2-benzylmalonate (1.0 equiv), NaH (3 equiv); (ii) 8a,b (1.7 equiv), THF, rt. (h) (i) 2-Vinylnapththalene (1.0 equiv), TMSCl (3 equiv), 8a,b (2.2 equiv); (ii) DBU (6 equiv), MeCN, rt. (i) (i) Phenylacetylene (1.0 equiv), n-BuLi (1.1 equiv); (ii) 8a,b (1.2 equiv), THF, –78 ºC. (j) (i) 4-Bromo-1,1′-biphenyl (1.0 equiv), n-BuLi (1.1 equiv); (ii) 8a,b (1.2 equiv), THF, –78 ºC. (k) (i) tri-O-Benzyl-D-glucal (1.0 equiv), 3 Å MS, TMSCl (3 equiv), 8a,b (2.2 equiv); (ii) DBU (6 equiv), MeCN, rt. (l) (1S,2R)-(+) -Norephedrine (1.0 equiv), 8a,b (3 equiv), CH$_2$Cl$_2$, rt. (m) Fluoxetine (1.0 equiv), 8a,b (1.5 equiv), Et$_3$N (1.1 equiv), CH$_2$Cl$_2$, rt. (n) (i) Donepezil (1.0 equiv), KHMDS (1.3 equiv); (ii) 8a (1.3 equiv), THF, –78 ºC. (o) Piperine (1.0 equiv), 8a (2.2 equiv), TMSCl (1.2 equiv), CH$_2$Cl$_2$, rt. (p) Ketorolac (1.0 equiv), 8a (2.0 equiv), TMSCl (2 equiv), CH$_2$Cl$_2$, rt. (q) rac-Naproxen (1.0 equiv), 8a,b (1.5 equiv), TFOH (1.2 equiv), CHCl$_3$, 40 ºC (for 25a) or 70 ºC (for 25b). Isolated yields given. Yields in parenthesis were determined by $^{19}$F NMR using 1,4-difluorobenzene (DFB) as internal standard (see the ESIF† for details). MS = molecular sieves, TFOH = trifluoromethanesulfonic acid, HMDS = hexamethyldisilazane, THF = tetrahydrofuran, TMS = trimethylsilyl, DBU = 1,8-diazabicyclo(5.4.0)undec-7-ene.

Both reagents showed robust stability not only in the solid state but also in solution. No detectable decomposition in non-polar solvents after heating up to 50 ºC for prolonged reaction times (> 1 week) was observed for 8a. In contrast, some polar (DMF, THF) and protic (H$_2$O) solvents promote slight to high decomposition rates, which are accelerated by temperature (Fig. S1, ESIF†). Moreover, differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) demonstrated the thermal stability of reagents 8a,b (Figs. S2 and S3, ESIF†).

Reaction Scope

With the optimal reagents in hand, their applicability was first evaluated with representative nucleophiles (Scheme 1A). First, a preliminary solvent compatibility study of 8a with N-H indole demonstrated that solvents of different nature
(chlorinated, aprotic polar, and aprotic non-polar solvents) do not substantially affect the performance of the reaction with yields of 9a up to >95% (Fig. S4, ESI†). Thus, reaction of N-H indole in CH2Cl2 with 8a,b afforded 9a (99%) and 9b (85%) after heating at 40 °C for 1 h or 24 h, respectively. Reaction with phenol required the addition of TfOH as a promoter and afforded 10a (97%) and 10b (86%). Next, we assayed the suitability of other nucleophiles to afford N–, O–, and S–SR bonds.28 Thus, reaction with benzylation gave the desired products 11a (93%) and 11b (87%) after 1 h at room temperature, while reaction with 2-mercaptobenzoxazole afforded instantaneously disulfides 12a (99%) and 12b (89%). Unlike phenol, which required a protic acid to activate the electrophilic reagent, preliminary results with alcoholic nucleophiles indicate the necessity of an exogenous base (e.g., Et3N) to deprotonate the hydroxyl moiety and deliver the desired products. Thus, adamantol derivatives 13a (91%) and 13b (89%) were obtained after 1 h at room temperature, using Et3N as a base. Reactions with the preformed enolate of 2,2-dimethylcyclopentanone afforded the double substitution products 14a (53%) and 14b (38%). Attempts to selectively obtain the monosubstituted product were unsuccessful due to the increased reactivity of the monosubstituted intermediate. Treatment of diethyl benzylation with sodium hydride (NaH) and subsequent reaction with 8a,b afforded 15a and 15b in 88% and 71% yield, respectively. Alkenes are also suitable nucleophiles as demonstrated with 2-vinylphththalene, using an addition/elimination sequence that afforded E/Z mixtures (up to 96:4) of vinylic SCF2CF3H 16a (99%) and SCF2CF3 16b (56%). Whilst treatment of phenylacetylene with 8a in the presence of CuBr failed to deliver the desired product,18 reaction of the alkyne with n-BuLi and subsequent reaction with 8a,b rendered 17a (84%) and 17b (>95%). Similarly, generation of the organolithium intermediate from 4-bromobiphenyl by lithium-bromine exchange afforded 18a (70%) and 18b (62%) after subsequent reaction with 8a,b.

Next, having demonstrated the versatility of our reagents with model nucleophiles, we aimed to evaluate their efficiency for the direct/late-stage modification of natural products and pharmaceuticals (Scheme 1B).29 First, the aforementioned addition/elimination protocol also worked well for the benzyl-protected D-glucal to afford 19a (80%) and 19b (78%).30 Interestingly, despite the large volume of SCF2CF3 and SCF2CF3H groups, they have less impact on the conformation of 2-substituted-D-glucals than their alkyl (e.g., CF3CF3, CF3) counterparts as indicated by the analysis of diagnostic coupling constants J1,4 = 4–4.6 Hz and J4,5 = 5–5.8 Hz (intermediate conformation deformed towards the 5H4) (Fig. S7, ESI†).31,32 (+)-Norephedrine was chemoselectively N-modified to 20a (59%) and 20b (90%) under mild reaction conditions without competitive O-substitution. The secondary amine of fluoxetine (Prozac™) also reacted successfully to deliver 21a,b in 77% and 87% yield, respectively. Donepezil, a drug used in the treatment of Alzheimer’s disease, was reacted with potassium bis(trimethylsilyl)amide (KHMDS) to generate the enolate that subsequently reacted with 8a to afford 22a in an excellent 99% yield. Similarly to 2-vinylphththalene and D-glucal, the use of the same addition/elimination protocol with piperine (black pepper alkaloid) and 8a in the presence of trimethylsilyl chloride (TMSCl) as a promoter, afforded 23a as a separable mixture of E/Z-isomers 23aE (66%) and 23aZ (15%), resulting from the modification of the conjugated diene system as determined by NMR and X-ray (for the E-isomer)9 analysis. Reaction of 8a with ketorolac, an anti-inflammatory agent, afforded 24a (87%) with the exclusive modification of the pyrrole moiety thus, demonstrating the compatibility of our reagent 8a with carboxylic acids. Finally, when naproxen was reacted with 8a and TfOH as a promoter, 25a (93%) was obtained as an 81:19 mixture of C10/C17 regioisomers. In contrast, reaction with 8b afforded 25b (92%) as the sole C10-isomer.
**Fig. 3** Multigram-scale preparation of tetrafluoroethylthio indoles (**panel A**) and derivatization reactions (**panel B**). See the ESI† for details. Boc = tert-butoxycarbonyl, DMF = N,N-dimethylformamide, HMDS = hexamethyldisilazane, TFA = trifluoroacetic acid.

**Large Scale and Derivatization**

Next, multigram-scale reactions (20 mmol) with a series of unprotected and N-Me-protected indoles afforded gram amounts of the corresponding SCF₂CF₂H-analogues 9a, 26a, and 27a with yields up to 99% (Fig. 3A). Notably, reaction crudes are substantially clean and only excess of 8a and saccharine are observed, which indeed can be simply removed by sequential washings with aqueous Na₂CO₃. Because the 1,1,2,2-tetrafluoroethylthio moiety represents an interesting platform for accessing other compounds, various derivatization reactions were evaluated (Fig. 3B). First, sulfenamide fluoxetine derivatives 21a,b were oxidized to sulfonamides 28a (56%) and 28b (75%) using H₂O₂ and a molybdenum catalyst. This methodology represents an overall workable strategy to obtain uncommon, fluorinated sulfonamides (Fig. 3B, upper panel). Noteworthy, the same oxidation conditions could be applied to the oxidation of thioether 9a to the corresponding sulfone 29a (95%) (Fig. 3B, lower panel). Next, after N-Boc protection of indole 9a to 30a (Boc₂O, Et₃N, CH₂Cl₂, rt, 16 h, 97%), the SCF₂CF₂H moiety of product 30a was deprotonated with KHMS and the resulting carbanion quenched with benzophenone. Finally, N-Boc removal with TFA gave access to CF₂CF₂-bridged 31a in 76% yield (suitable for X-ray diffraction). This strategy serves as a proof of concept for the functionalization with electrophiles of terminal SCF₂CF₂H-containing compounds. Finally, Suzuki cross-coupling of 5-bromoindole 26a with an aryl boronic
acid partner smoothly afforded 32a in an excellent 90% yield, thus demonstrating group compatibility with Pd-catalyzed transformations.

Conclusions
In summary, two new reagents for the direct introduction of SCF$_2$CF$_2$H and SCF$_2$CF$_3$ motifs have been disclosed. These electrophilic agents are synthetized in three steps from simple and readily available starting materials and can be obtained in a multigram scale. Electrophilic introduction has proven successful in a range of different nucleophiles, including amines, alcohols, thiols, electron-rich (hetero)aromatics, phenols, ketones, 1,3-diesters, and alkenes as well as organolithium alkyne and arene derivatives. The robustness of the transformation, including its operational/purification simplicity has been further demonstrated with a range of complex structures, including blockbuster drugs and natural products. Gram-scale reactions and product derivatization to sulfones, sulfonamides, and deprotonation of SCF$_2$CF$_2$H-addition to electrophiles as well as orthogonal metal-mediated reactions have also been demonstrated. We expect our findings will provide new opportunities in drug and agrochemical discovery by expanding the toolbox of reagents for the introduction of new fluorinated motifs into natural products and active ingredients.

Author Contributions
J.M and M.B. performed all the experiments. O.B. supervised the project. O.B. and S.C. were responsible for funding acquisition. All the authors contributed to the preparation of the manuscript.

Conflicts of interest
The authors are co-inventors on a patent application (PCT/EP2021/067690) that incorporates discoveries described in this manuscript.

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Notes and references

§ CCDC deposition numbers 2099949 (8a), 2099951 (8b), 2099950 (23aE), and 2099948 (31a) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.


10 Electrostatic potential surfaces were calculated after geometry optimization at the CPCM (water) B3LYP/6-311+G(d,p) level of theory using Gaussian09, M. J. Frisch et al. See the ESI† for full reference.


