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Chemoselective Perfluoromethylation of Thio- and Selenoamides

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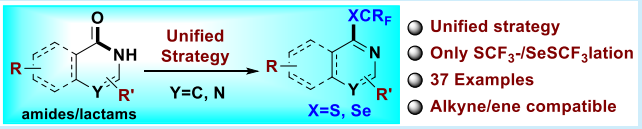
ABSTRACT: A chemo- and regioselective perfluoromethylation using thioamides/selenoamides (prepared one step from corresponding lactams) as starting materials has been discovered. The reaction demonstrated complementary chemoselectivity to the C−H trifluoromethylation of (hetero)arenes as well as remarkable functional group compatibility especially toward radical sensitive olefin-, alkyne-, and arylhalide-bearing substrates. The examples of perfluorothio-/selenolated drug molecules indicated application potential of this strategy in drug modification and drug-analogue preparation.



Chemo- and regioselective introduction of perfluoromethylthio- (SCR_F) and perfluoromethylseleno- ($SeCR_F$) groups had become an emerging demand in small molecule drug (SMD) development within both academia and the pharmaceutical industry,[1] due primarily to their improvement to the metabolic stability[2] and cell membrane permeability by enhancing lipophilicity,[1e] while possessing the electronic property of a drug lead. A statistical fact is that most SMDs contain nitrogen-enriched heterocycles,[2c,d] which renders the precise chemical modification of heterocycles an everlasting theme in medicinal chemistry especially with biologically relevant molecules (exemplified by the antibiotic 5′-SCF_3 adenosine[3] and marketed acaricide Vanliniprole[4] in Figure 1), with emerging horizons expanding to RNA−protein interaction detectors such as 2′-SCF_3 uridine (Figure 1).[5]

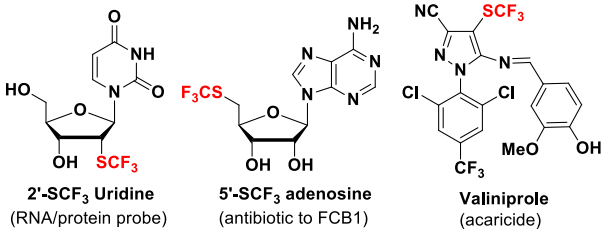


Figure 1. SCF_3-containing chemical probes and drug candidates.

In this context, different strategies and reagents had been developed to introduce SCF_3 groups directly and indirectly.[6,7] Among these, the inexpensive and stable CF_3SO_2Na[8] was widely used as the CF_3 source in the trifluoromethylation (CF_3lation) protocol that reacts with thiophenols and disulfides[9] to generate the corresponding SCF_3 moiety pioneered by the Langlois group (Figure 2a).[8] Direct trifluoromethylthiolation of nonprefunctionalized heterocycles is uncommon[10] not to mention the elusive trifluoromethylselenolation using CF_3SO_2Na.[11] A single seminal example using a rare thiohydroxamic ester was reported by Barton through a photon-initiated decarboxylative rearrangement (Figure 2b).[12]

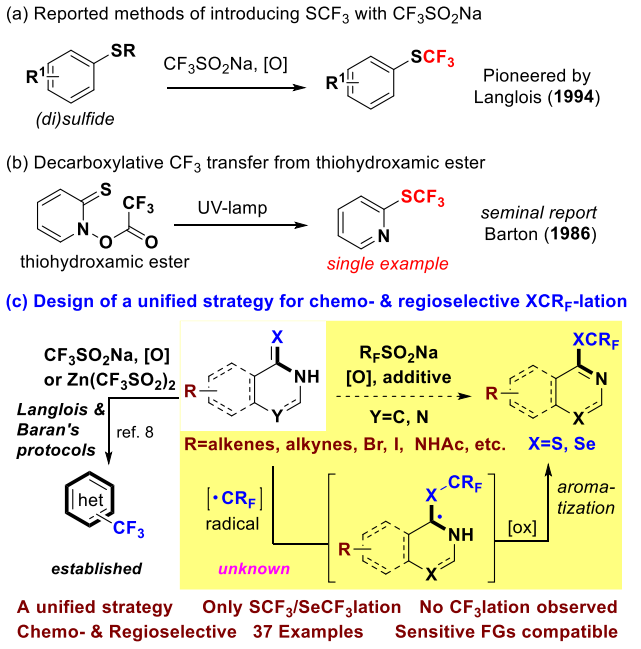


Figure 2. Design of a unified strategy for chemoselective perfluoromethylthiolation and perfluoromethylselenolation.

Inspired by these, a unified strategy to chemo- and regioselectively introduce SCR_F and $SeCR_F$ groups into biologically important nucleosides or N-heterocycles based on

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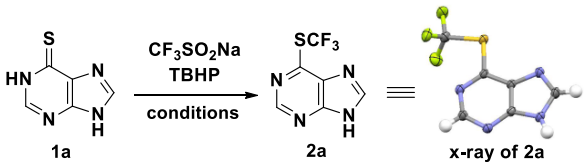
the benchtop R_fSO_2Na salts was pursued with the hope of showing complementary chemoselectivity toward the previously known C−H trifluoromethylation process by Baran and co-workers (Figure 2c, left part).[13]

Our design (Figure 2c) focused on a neglected yet ubiquitous functional group, amides and/or lactams, which can be readily converted to thioamides and selenoamides using P_2S_5 and Woollins' reagent,[14] respectively. We postulated that the *in situ* generated CR_F radical would chemoselectively attack the atom X instead of olefins/heterocycles, *due hypothetically to the more stable resulting ketyl radical as well as the electrophilically polarizable thionyl/selenyl group*. The delocalized ketyl radical could be readily oxidized and aromatized to yield products that bear XCR_F at the *ortho* position of the N-heterocycles (Figure 2c). This design faces two grand challenges: (1) control the reactivity of the X group over olefins and/or heteroarenes toward CR_F radicals; (2) competitive oxidation of thio-/selenoamides over CR_FSO_2Na salts under oxidative conditions.[15]

To test our hypothesis, the commercially available mercaptopurine **1a** was used to determine the reaction conditions (Table 1). The initial attempt was carried out using CF_3SO_2Na, in DCM at 40 °C. Gratifyingly, only the desired 6-SCF_3 purine **2a** was isolated albeit in 29% yield with 61% conversion (entry 1, Table 1). Given the fact that solvents played an important role in this type of reaction, several solvents were screened ranging from nonpolar toluene (35% yield, entry 2) to protic EtOH (25% yield, entry 3); the yields varied, but the mass balance was not satisfactory. Astonishingly, using DMF and THF almost shut down the desired reaction pathway (entries 4 and 5), and significant decomposition was observed for the above trials (entries 1−5). Serendipitously, when the EtOAc was used as solvent, the isolated **2a** reached a 56% yield, due to the better solubility of the sodium salt (entry 6). The acetone proved to be the optimal solvent, as **2a** was obtained in 63% yield. The temperature was determined to cause decomposition of **1a** by accelerating CF_3SO_2Na oxidation. The reaction proceeds sluggishly at room temperature with a slight drop in yield (53%, entry 8). The copper salt additive is essential to the reaction, as a significant drop in efficiency would result if no copper is used (22% yield, entry 9). Other copper salts were screened (entries 10−12) revealing CuI as the optimal choice, which yielded 85% of **2a** (entry 13). Crystallography of **2a** (CCDC 2011317) showed its unambiguous structure and substituted pattern (Table 1). No traditional C_2−CF_3 products had been detected (see Supporting Information, SI, for details).

Table 1. Selected Condition Optimization



Entry[a]	Cu additive	Solvent	Conversion[b]	Yield[c]
1	Cu powder	DCM	61%	29%
2	Cu powder	Toluene	76%	35%
3	Cu powder	EtOH	100%	25%
4	Cu powder	DMF	100%	0%
5	Cu powder	THF	100%	13%
6	Cu powder	EtOAc	100%	56%
7	Cu powder	Acetone	100%	63%
8[d]	Cu powder	Acetone	100%	53%
9	none	Acetone	100%	22%
10	$CuCl_2$	Acetone	100%	37%
11	$Cu(OTf)_2$	Acetone	100%	67%
12	CuCN	Acetone	100%	61%
13	CuI	Acetone	100%	85%

[a]All reactions were run with copper salt (0.2 equiv), CF_3SO_2Na (2.0 equiv), and TBHP (2.0 equiv) on a 0.5 mmol scale of **1a** under air in solvents at 40 °C for 1 h unless otherwise noted. [b]Conversions were determined based on recycled starting material after isolation. [c]Isolated yield. [d]Room temperature for 4 h; TBHP = *tert*-butyl hydroperoxide (70% in water).

With the optimal conditions in hand, the substrate scope was examined (Table 2). First, the reaction proceeded smoothly with alkyl substituted mercaptopurine bearing methyl (**1b**), ethyl (**1c**), isopropyl (**1d**), isobutyl (**1e**), and benzyl (**1f**) on nitrogen. Desired SCF_3 products **2b**−**2f** were obtained in good yields (62−76%, entry 2). No obvious electronic effects can be deduced. When cyclopropyl-containing **1g** was subjected to the standard reaction conditions, a 54% yield of **2g** was isolated and cycloproyl group was well preserved (entry 3). Benzyl ether (**1h**) and even free alcohol (**1i**) could be well tolerated, providing **2h** and **2i** in 71% and 81% yield, respectively (entries 4 and 5). Based on this result, we tested the traditionally radical intercepting group such as alkene and alkyne bearing substrate **1j** and **1k**. Surprisingly, both olefin (**2j**, 46% yield) and alkyne (**2k**, 56% yield) were untouched under the reaction conditions (entries 6 and 7), demonstrating the chemoselective feature of this reaction. The sterically varied environment near the reacting thioamides were created by attaching different groups on to the N9-poisition (**1l**−**n**). A significant decrease in yield was observed (from 57% to 0%), with **1n** as a completely inert substrate (entry 8). The C8-cyclohexyl substituted **1o** afforded a 55% yield of **2o** (entry 9). The thioguanine-based **1p** and **1q** served as good precursors and yielded **2p** and **2q** in 78% and 57% yield, respectively (entries 10 and 11). The unprotected free amine might be the reason for the decreased efficiency of the latter. 6-Thioallopurinol (**1r**) and its Bn protected regioisomers (**1s** and **1t**) all led to desired products (**2r**−**2t**) in synthetically useful yields (60−65%, entries 12−14).

To further expand the substrate scope, 4-thio-quinazolinone **1u** was subjected to the reaction conditions. Delightedly, the corresponding 4-SCF_3 quinazoline **2u** was obtained in 72% yield. The radical sensitive aryl halide **1v** was a viable substrate and yielded **2v** in 57% yield (entries 15 and 16). The skeletal-tuned thiopyrimidone substrates **1w** and **1x** resulted in increased yields (**2w**, 75% and **2x**, 68%), due probably to the increased electron density of the core heterocycle (entries 17 and 18). The isoquinolinethione-type precursors also proved to be viable, providing products **2y** (56%) and **2z** (62%) in moderate yields (entries 19 and 20). Based on the above results, we attempted to modify drug-like precursors (entries 21−24). The triacylated thioinosine **1aa**, which acted as a highly antineoplastic and immunosuppressive metabolite, could be successfully transformed to its SCF_3 counterpart **2aa** in 63% yield. This paved the way for transforming antiviral drug acyclovir analogue (**1ab**) and ganciclovir analogues (**1ac**) into their SCF_3 products **2ab** (73%) and **2ac** (67%) yields, respectively. 6-Mercaptopurine riboside (**1ad**) was converted to the desired **2ad** and its acetone-masked form **2ad′** in a combined 85% yield under standard conditions, indicating the practicality of this method in modifying drug candidates.

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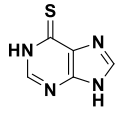
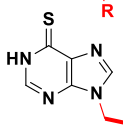
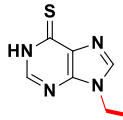
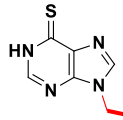
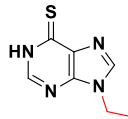
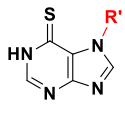
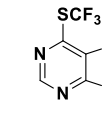
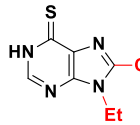
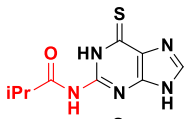
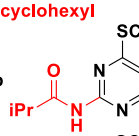
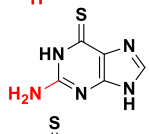
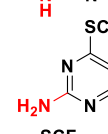
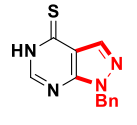
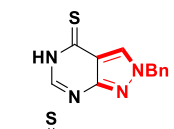
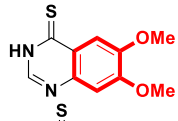
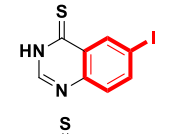
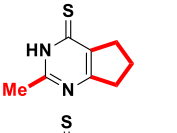
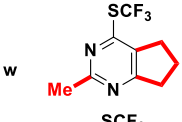
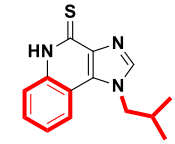
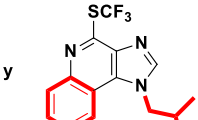
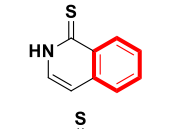
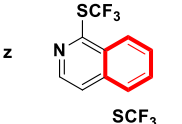
Table 2. Substrate Scope of Trifluoromethylthiolation[a]

Entry	Substrate	Product	Yield[b]
1	 1a	 2a *x-ray obtained*	85%
2	 1b-f	 2b, R=Me 2c, R=Et 2d, R=*i*Pr 2e, R=*i*Bu 2f, R=Bn	68% 62% 76% 73% 62%
3	 1g	 2g *x-ray obtained*	54%
4[c]	 1h	 2h	71%
5	 1i	 2i	81%
6	 1j	 2j	46%
7	 1k	 2k	56%
8	 1l-n	 2l, R'=Me 2m, R'=Et 2n, R'=iPr	57% 49% 0
9	 1o Et Cy=cyclohexyl	 2o	55%
10	 1p	 2p *x-ray obtained*	78%
11	 1q	 2q *x-ray obtained*	57%
12	 1r	 2r	62%
13	 1s	 2s	65%
14	 1t	 2t	60%
15	 1u	 2u	72%
16	 1v	 2v	57%
17[c]	 1w	 2w	75%
18[c]	 1x	 2x	68%
19	 1y	 2y	56%
20	 1z	 2z	62%
21	1aa	2aa	63%
22	1ab	2ab	73%
23	1ac	2ac	67%
24	1ad	2ad (50%) 2ad'(35%)	

[a]All reactions were run with CF_3SO_2Na (2.0 equiv), TBHP (2.0 equiv), CuI (0.2 equiv) on a 0.2−1.0 mmol scale of **1** in acetone (3.0 mL) at 40 °C for 1 h unless otherwise noted. [b]Isolation yield. [c]The reactions were run with CF_3SO_2Na (4.0 equiv), TBHP (4.0 equiv), Cu powder (0.2 equiv) in EtOAc (3.0 mL) at 40 °C for 2 h.

With the established conditions in hand, perfluoromethylation on selenoamides **3** was attempted (Table 3). First sterically different **3a−3c** were prepared (see SI for detail), and the anticipated $SeCF_3$ purines **4a−4c** were successfully isolated in

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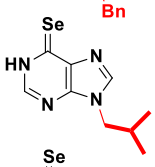
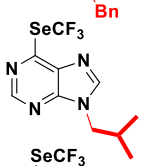
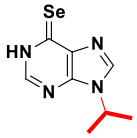
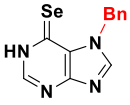
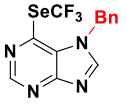
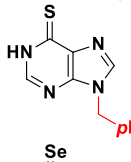
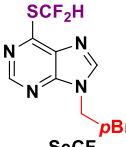
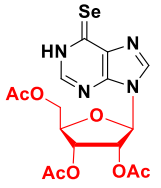
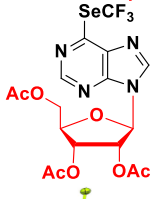
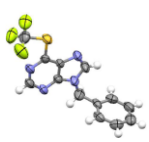
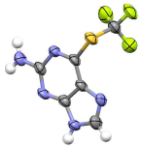
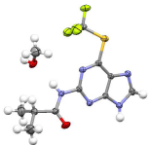
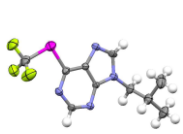
Table 3. Substrate Scope for $SeCF_3$ and XCF_2H

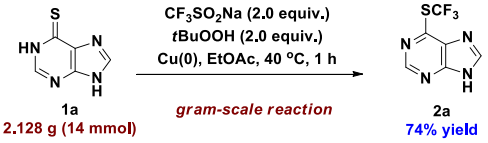
Entry[a]	Substrate		Product		Yield[b]
1		3a		4a	75%
2		3b		4b	72% X-ray analyzed
3		3c		4c	63%
4		3d		4d	25%
5[c]		3e		4e	61%
6[c]		3f		4f	64%
7		3g		4g	62%
	 x-ray of 2f		 x-ray of 2q		 x-ray of 2p  x-ray of 4b

[a]All reactions were run with CF_3SO_2Na (2.0 equiv), TBHP (2.0 equiv), and Cu powder (0.2 equiv) on a 0.2−1.0 mmol scale of **3** in ethyl acetate (3.0 mL) at 40 °C for 1 h. [b]Isolation yield. [c]CF_2HSO_2Na (2.0 equiv) was used.

good yields (63−75% yield). The slightly decreased yields might be caused by increasing steric hindrance (entries 1−3). When a Bn protected **3d** was attempted, only a 25% yield of **4d** can be obtained, demonstrating the steric sensitivity of this reaction (entry 4). X-ray crystallography of products **2f**, **2p**, **2q**, and **4b** (CCDC 2011139, 2011318, 2011319, and 2011320) were obtained verifying their substituted pattern (Table 3). Difluoromethylthio-/selenolation had been an emerging research topic,[16] as it serves in the fine-tuning of the XCF_3 analogues in medicinal evaluations. Our methodology proved to be a robust protocol to introduce $SeCF_2H$ and SCF_2H groups on to a purine skeleton as well, since products **4e** and **4f** were both isolated in 61% and 64% yield, respectively (entries 5 and 6). The fact that obtaining **4g** (62% yield) demonstrates that the bioactive and drug-like molecules can be $SeCF_3$lated in good yield and no CF_3 product can be found (entry 7).

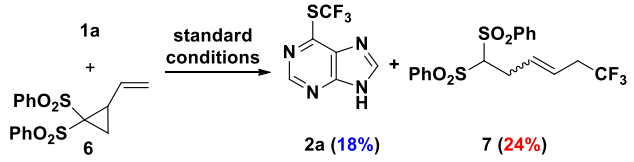
To highlight the practicality of this method, **1a** was reacted on a 2-g scale and the reaction maintained its efficiency (**2a**, 74% yield, Scheme 1). The survival of radical sensitive alkynes/

Scheme 1. Gram-Scale Reaction



olefins together with the experimental fact that no CF_3 products could be detected prompted us to test whether any radical species were generated in the reaction process. A radical-scavenging substrate **6** (Scheme 2) was added in the reaction

Scheme 2. A Radical Clock Experiment



vessel. It was found that trifluoromethylthiolation was retarded (**2a**, 18% yield) and CF_3 radical was successfully intercepted (**7**, 24% yield). Based on these results we tentatively propose that the reaction proceeds as depicted in Figure 2c.

In summary, a unified strategy using copper-mediated chemoselective perfluoromethylation/aromatization cascade reactions of thioamides and selenoamides has been developed. Various $-XCR_F$ containing heterocycles (37 examples) have been obtained with moderate to good yields. This protocol is complementary to the well-known arene C−H trifluoromethylation process. Radical sensitive functional groups such as olefins and alkynes are well tolerated. This is the first report of using thio- and/or selenoamides to achieve $-XCR_F$ heterocycles. We look forward to its application in medicinal research.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03241.

Experimental procedures; spectral data (PDF)

Accession Codes

CCDC 2011139 and 2011317−2011320 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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