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Letter

Synthesis of Fluorinated Amide Derivatives via a Radical N-Perfluoroalkylation–Defluorination Pathway

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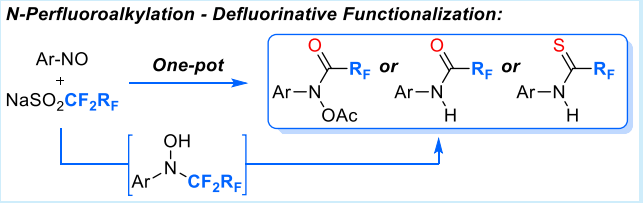
ABSTRACT: A one-pot approach to fluorinated hydroxamic acid, amide, and thioamide derivatives is reported. The reaction proceeds via an N-perfluoroalkylation of nitrosoarenes with perfluoroalkanesulfinates, resulting in labile N-perfluoroalkylated hydroxylamines. By the addition of suitable additives, a controllable oxy/thiodefluorination of the fluorinated hydroxylamine intermediates was achieved. The method highlights N-perfluoroalkylated amines as versatile intermediates for further synthesis.

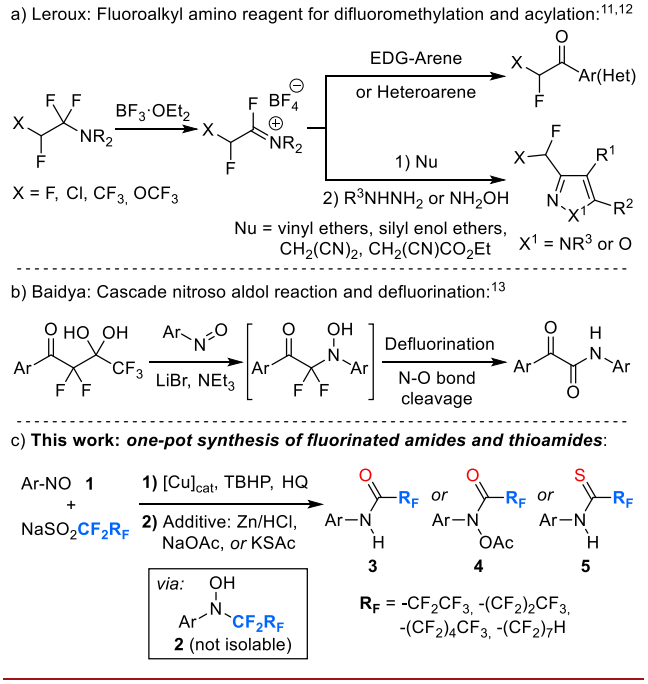


The incorporation of fluorine into organic compounds has become increasingly important for pharmaceutical and agrochemical sciences as the presence of a fluorinated moiety can drastically change physical, chemical, and biological properties.[1] Thus, a large number of methods for the direct introduction of perfluoroalkyl groups (most commonly CF_3 groups), onto C-, O-, and S-atoms[2] via electrophilic,[3] nucleophilic,[4] and radical[5] pathways have been reported. The corresponding N-perfluoroalkylation is, however, less investigated.[6] One reason is the poor stability of perfluoroalkylated amines, as they are prone to fluoride elimination, assisted by the nitrogen lone pair,[7] resulting in highly electrophilic fluoroiminium species. Although the high reactivity of these intermediates is challenging to control, the synthesis and direct utilization of perfluoroalkyl amino compounds is an attractive method for the diversification of fluorinated compounds.

Since the seminal work of Yarovenko,[8] Ishikawa,[9] and Petrov[10] on the *in situ* preparation of fluorinated ethylamine and its use as a fluorination agent for the conversion of alcohols into alkyl fluorides, the direct functionalization of perfluoroalkyl amines has received limited attention. Recently, Leroux reported an elegant method for the activation of fluorinated ethylamines via fluoride abstraction by a Lewis acid (e.g., $BF_3{\cdot}OEt_2$) to afford relatively stable iminium salts.[7c] The nucleophilic addition of electron-rich arenes or heteroarenes enabled the synthesis of various aryl or heteroaryl fluoromethyl ketones (Scheme 1a).[11] Furthermore, trapping with electron-rich olefins or C–H acidic compounds, followed by cyclization with hydrazine or hydroxylamine, provided access to a wide range of fluorinated pyrazoles and isoxazoles.[11,12]

A recent report by Baidya and co-workers disclosed an N-selective nitroso aldol reaction between *gem*-difluoroenolates and nitrosoarenes. The difluoroalkyl intermediate underwent an intramolecular nucleophilic substitution, followed by a rearrangement via C–F and N–O bond cleavage to furnish α-ketoamides (Scheme 1b).[13]

Scheme 1. Defluorination of Fluorinated Amines



Despite the above-mentioned progress, novel reactivity discoveries of perfluoroalkyl amines are still rare, and the direct transformation of these intermediates incorporating a

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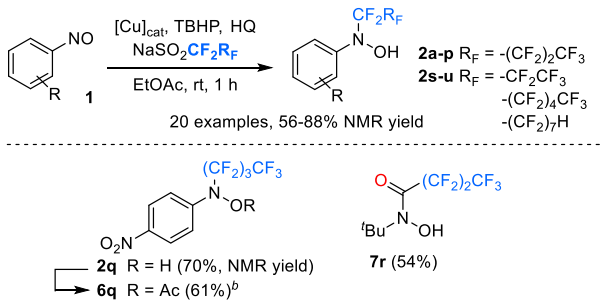
controllable defluorination process is desirable. Recently, we developed a radical N-trifluoromethylation of nitrosoarenes[6b] with sodium triflinate to obtain a range of isolable N-trifluoromethylated hydroxylamines. However, when longer-chain perfluoroalkanesulfinates[5a,14] were used, we observed a decomposition of the perfluorinated hydroxylamine upon attempted isolation. As one of the decomposition products was identified as a hydroxamic acid derivative (formal oxydefluorination at the α-position), we set out to investigate a controllable defluorination. Notably, fluorinated amides are important motifs in biologically active molecules[15] and valuable building blocks for pharmaceuticals,[16] dyes,[17] and functional materials.[18] Only a few synthesis methods for perfluorinated amides are reported;[15b,17,19] most of them have a limited substrate scope and rely on sensitive acid derivatives or coupling reagents.

Herein, we report a one-pot N-perfluoroalkylation reaction of nitrosoarenes for the synthesis of fluorinated hydroxamic acids, amides, and thioamides via N-perfluorinated hydroxylamine intermediate **2** (Scheme 1c).

We first investigated the scope of the perfluoroalkylation reaction with respect to various nitrosoarenes and sodium perfluoroalkanesulfinates (for details, see the SI, Table S-1). As judged by ^{1}H NMR, a variety of nitrosoarenes bearing either electron-withdrawing or electron-donating substituents at the *ortho-*, *meta-*, or *para-* positions were transformed into the corresponding hydroxylamines in moderate to high yields (**2a**–**2q**, 56–88% by NMR). In addition, the sodium sulfinate component could be varied to include both shorter (perfluoropropyl) and longer (8*H*-perfluorooctyl) perfluoroalkyl chains (**2s**–**2u**, 68–80%, Scheme 2).

Scheme 2. N-Perfluoroalkylation of Nitroso Compounds[a]

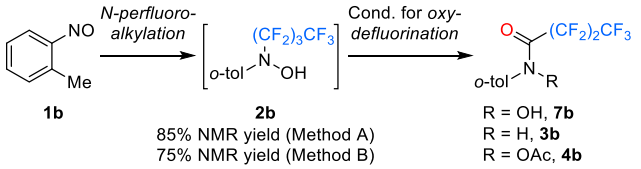


[a]General Conditions: **1** (0.50 mmol), $NaSO_2CF_2R_F$ (1.5 mmol), hydroquinone (0.55 mmol), $Cu(ClO_4)_2{\cdot}6H_2O$ (1 mol %), EtOAc (4.0 mL), and ^{t}BuOOH (70% aq, 1.5 mmol). [b]After adding Ac_2O (1.0 mL) and $NaHCO_3$ (3.0 mmol), stirring for 24 h, isol. yield.

Although the hydroxylamines **2** were not isolable, electron-deficient hydroxylamine products were found to be more stable; acetylated hydroxylamine **6q** could be isolated in 61% yield after the acetylation of **2q** (Scheme 2). An aliphatic nitroso compound was a suitable substrate as well. However, the corresponding hydroxylamine was found to be the least stable; oxydefluorinated product **7r** was obtained in 54% isolated yield, instead of the expected hydroxylamine.

Intrigued by the oxydefluorination reaction observed for product **7r** and the relative stability of hydroxylamines **2** in solution, we set out to find general conditions facilitating the oxydefluorination in a one-pot process. As shown in Table 1, stirring the reaction mixture at a higher temperature for an extended time was beneficial for the oxydefluorination, yielding hydroxamic acid **7b** in 25% yield (entry 1).

Table 1. Condition Screening for Oxydefluorination[a]



entry	conditions for oxydefluorination	yield **7b** (%)[b]	yield **3b** (%)[b]	yield **4b** (%)[b]
1	50 °C, 24 h	25	-	-
2[c]	HCl (20 equiv), rt, 6 h	36	-	-
3[c,d]	HCl (20 equiv), HOAc, 0 °C, 6 h	41 (35)[e]	-	-
4	$InCl_3$ (3 equiv), 50 °C, 6 h	26/24[f]	-	-
5	$BF_3{\cdot}OEt_2$ (10 equiv), rt, 6 h	24[f]	-	-
6[c,d]	Zn/HCl (40 equiv), HOAc, 65 °C, 6 h	-	72 (70)[e]	-
7	NaOAc (6 equiv), rt, 16 h	-	-	69 (64)[e]
8[f]	NaOAc (6 equiv), rt, 16 h	-	-	68 (64)[e]

[a]Method A: **1b** (0.10 mmol), $NaSO_2(CF_2)_3CF_3$ (0.3 mmol), hydroquinone (0.11 mmol), $Cu(ClO_4)_2{\cdot}6H_2O$ (1 mol %), EtOAc (0.8 mL), and ^{t}BuOOH (70% aq., 0.3 mmol), rt, 1 h. [b]^{19}F NMR yields determined with HFIP as an internal standard. [c]37% HCl was used. [d]1.0 mL of HOAc was used. [e]Isolated yield (0.5 mmol). [f]Method B: $CuCl_2$ (5 mol %) and ^{t}BuOOH (55% in decane, 0.3 mmol) were used instead of $Cu(ClO_4)_2{\cdot}6H_2O$ and aq. ^{t}BuOOH.

We then screened a variety of Brønsted and Lewis acids for their effects on the oxydefluorination (see also the Supporting Information). Using HCl as a promoter led to an increased yield of **7b** (36%, entry 2), while AcOH as a cosolvent resulted in a slight improvement: the reaction at 0 °C afforded hydroxamic acid **7b** in 41% yield (35% isolated, entry 3). Our attempts to use $InCl_3$ or $BF_3{\cdot}OEt_2$ as promoters were unsuccessful, both when the perfluoroalkylation was conducted under nondry conditions (Method A) and when TBHP in decane (Method B) was used (entries 4 and 5). Gratifyingly, under acidic reductive conditions (Zn/HCl in AcOH), amide **3b** was obtained in 72% yield after oxydefluorination and N–O bond reduction (entry 6).

Furthermore, we examined the effect of bases on the oxydefluorination. While K_2CO_3 and pyridine led to decomposition, intermediate **2b** was converted into the corresponding O-acetylated hydroxamic acid using NaOAc. The unexpected product **4b** was isolated in 64% yield (entries 7 and 8).

It is worth to mention that when moderate yields were obtained, no evident side products were identifiable in these one-pot reactions. If the oxydefluorination was not efficient, the hydroxylamine intermediates decomposed, and complex mixtures were obtained.

Having evaluated the oxydefluorination of hydroxylamine intermediates **2**, we examined the scope of this one-pot protocol for the synthesis of amides **3** (Scheme 3).[20] Nitrosobenzene was transformed into amide **3a** in 55% yield via the one-pot perfluoroalkylation/oxydefluorination under reductive conditions. High yields were generally obtained for ortho-substituted amides (**3b**, **3e**, **3g**, and **3h**, 53–70%), with the exception of **3c** (42% yield). Halogen substituents were also well tolerated (**3g**–**j**, 53–70%). The meta-CF_3-substituted

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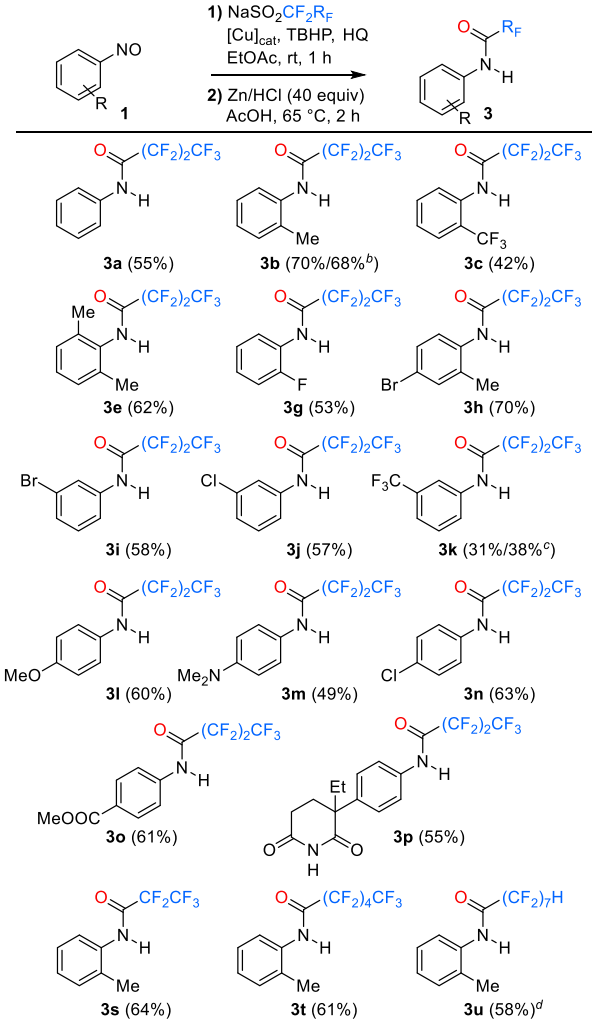
Org. Lett. 2020, 22, 2791–2796

Scheme 3. Synthesis of Amides 3 with Zn/HCl[a]



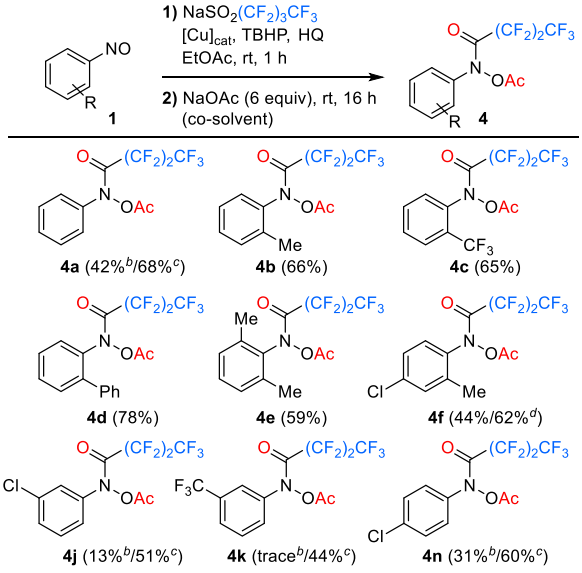
[a]Reaction conditions: Step (1) Method A (*cf.*, Table 1), 0.50 mmol scale. Step (2) HOAc (5 mL), Zn (powder, 20 mmol), and HCl (37% aq, 20 mmol) were added to the reaction mixture, 2 h at 65 °C. Isolated yields over two steps. [b]1.0 mmol scale. [c]Method B (*cf.*, Table 1) was used for Step (1), 0.50 mmol scale. [d]0.20 mmol scale.

amide **3k** was obtained in a low yield (31%, Method A), whereas dry conditions (Method B) led to a slightly higher yield (38%). A range of para-substituted amides were obtained in good yields (**3l**−**p**, 49−63%), including electron-rich (**3l** and **3m**, 60 and 49%) and electron-poor (**3n** and **3o**, 63 and 61%) arenes. Notably, aminoglutethimide derivative **3p** was obtained in 55% yield. Amides derived from other perfluoroalkanesulfinates were isolated in similar yields (**3s**−**u**, 58−64%).

The oxydefluorination reaction of ortho-substituted substrates, with sodium acetate as a promoter, delivered *O*-acyl hydroxamic acids **4b**−**f** in high yields (59−78%, Scheme 4). Electron-rich and electron-poor arenes as well as ortho-disubstituted substrates worked well using nondry reaction conditions (Method A). For product **4f**, the yield was improved from 44 to 62% by the addition of 1,1,2,2-tetrachloroethane (TCE) as a cosolvent.

However, for substrates lacking an *ortho*-substituent (**4a**, **4j**, **4k**, and **4n**), dry reaction conditions (Method B) and a cosolvent were necessary to obtain high yields. For example,

Scheme 4. Oxydefluorination with NaOAc[a]



[a]Reaction conditions: Step (1) Method A, 0.50 mmol scale. Step (2) NaOAc (3.0 mmol) was added to the reaction mixture, 16 h at rt. Isolated yields over two steps. [b]^{19}F NMR yields determined with HFIP as an internal standard, using Method A. [c]Isolated yields using Method B for Step (1), 0.50 mmol scale. DCM (4.0 mL) was added as a cosolvent in Step 2. [d]TCE (4.0 mL) was added as a cosolvent in Step 2.

only traces of **4k** were observed using Method A, whereas 44% yield was reached using Method B (Scheme 4).

In analogy with NaOAc, we next explored KSAc as an additive for the defluorinative functionalization. We envisioned that thioamide derivatives could be obtained under similar conditions. Such a procedure could serve as an alternative method for the synthesis of fluorinated thioamides.[21] Unlike the oxydefluorination with NaOAc, the thioacetate-promoted reaction led to the formation of thioamides **5**, involving a concomitant cleavage of the N−O bond. Additionally, dry conditions (Method B) had to be used in order to obtain the thioamide products (Scheme 5).

Substrates bearing *ortho*-substituents reacted smoothly, affording thioamides **5b** and **5c** in 68 and 63% yield, respectively. For other substrates, a cosolvent was required (**5a**, **5j**, **5k**, and **5o**). Nitrosobenzene was transformed into thioamide **5a** in 57% yield, whereas the meta-substituted thioamides **5j** and **5k** were obtained in slightly lower yields (47−50%). Ester derivative **5o** was isolated in 62% yield.

To demonstrate the applicability of our method, amide **3b** was reduced by $LiAlH_4$ into amine **9** in 65% yield. Furthermore, thioamide **5c** was efficiently transformed into benzothiazole **10** in 70% yield, via an oxidative cyclization using CAN.[22] The *S*-phenyl thioimidate **11** could be obtained in 88% yield from **5c** by reaction with a diaryliodonium salt (Scheme 6).[23]

A proposed mechanism for the defluorinative functionalization is presented in Scheme 7. The defluorination of hydroxylamine intermediate **2** is likely facilitated by the nitrogen lone pair[7,13] and hyperconjugation from the perfluoroalkyl group, yielding oxaziridine **A**.[24] Our attempts to detect intermediate **A** (by NMR and MS) were fruitless, as a rapid conversion into the products was observed. In the

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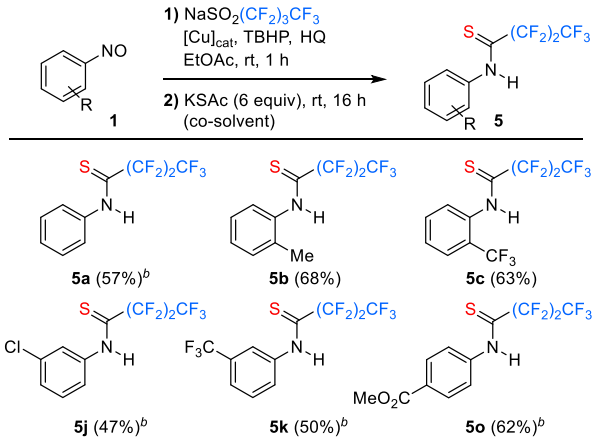
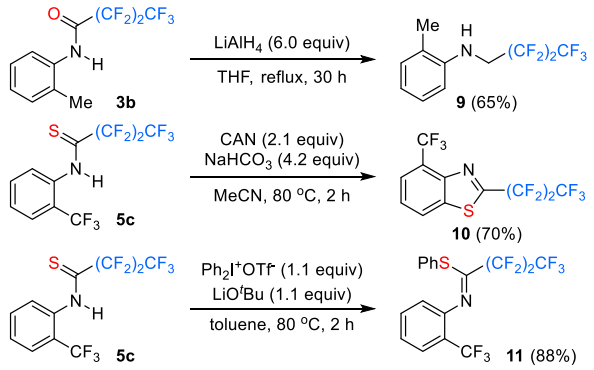
Org. Lett. 2020, 22, 2791−2796

Scheme 5. Synthesis of Thioamides 5[a]

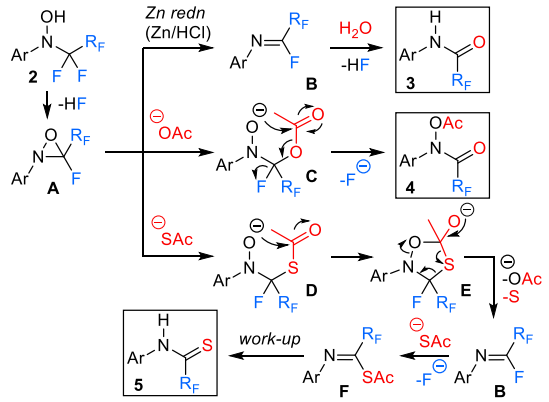


[a]Reaction conditions: Step (1) Method B, 0.50 mmol scale. Step (2) KSAc (3.0 mmol) was added to the reaction mixture 16 h, rt. Isolated yields over two steps. [b]DCM (4.0 mL) was added as a cosolvent in Step (2).

Scheme 6. Synthesis Applications



Scheme 7. Mechanistic Proposal



presence of Zn/HCl, **A** is reduced to iminoyl fluoride **B**, which after hydrolysis affords amide **3** (Scheme 7).

In the presence of sodium acetate, *O*-acyl hydroxamic acid **4** can be obtained via a nucleophilic attack by acetate, followed by a rearrangement of intermediate **C**. To confirm that the acetyl group originates from sodium acetate (and not EtOAc), the reaction was performed with sodium propionate, yielding *O*-propionyl hydroxamic acid **8b** in 44% yield (see the SI). When potassium thioacetate is used as a nucleophile, the opening of oxaziridine **A** by thioacetate gives intermediate **D**. An analogous rearrangement to **E**, followed by a cleavage of the N−O and C−S bonds,[25] affords iminoyl fluoride **B**, acetate, and sulfur. The subsequent nucleophilic addition of thioacetate gives intermediate **F**, which then is hydrolyzed to form thioamide product **5**. Upon GCMS analysis of the crude reaction mixtures for thioamides **5a** and **5b**, we detected the corresponding intermediates **F**, in support of our mechanistic hypothesis.

In summary, an efficient one-pot N-perfluoroalkylation−defluorination functionalization was developed. After perfluoroalkylation of the nitrosoarene starting materials, labile perfluoroalkyl hydroxylamines were obtained. Although not isolable, the hydroxylamine intermediates were readily converted into a variety of perfluoroalkylated amides, hydroxamic acids, and thioamides, through a controllable defluorination pathway. This work demonstrates the versatility of fluorinated hydroxylamines as intermediates for the synthesis of novel fluorine-containing targets.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00768.

Detailed experimental data and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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