Synthetic Methods

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Efficient Synthesis of Trifluoromethyl Amines through a Formal Umpolung Strategy from the Bench-Stable Precursor $(Me_4N)SCF_3$

*Thomas Scattolin, Kristina Deckers, and Franziska Schoenebeck**

Abstract: *Reported herein is the one-pot synthesis of trifluoromethylated amines at room temperature using the bench-stable* $(Me_4N)SCF_3$ *reagent and AgF. The method is rapid, operationally simple and highly selective. It proceeds via a formal umpolung reaction of the* SCF_3 *with the amine, giving quantitative formation of thiocarbamoyl fluoride intermediates within minutes that can readily be transformed to N-*CF_3*. The mildness and high functional group tolerance render the method highly attractive for the late-stage introduction of trifluoromethyl groups on amines, as demonstrated herein for a range of pharmaceutically relevant drug molecules.*

Fluorination confers molecules with improved properties and function, affecting lipophilicity, solubility, conformational and metabolic stability features that impact numerous branches of chemistry, including the agrochemical and pharmaceutical arenas.[1] While up to 40% of all active compounds feature at least one fluorine atom, nitrogen makes up for an even greater abundance of 80%.[2] In view of the widespread dissemination of both elements in pharmaceuticals, it is somewhat puzzling that their combined functionality, that is, trifluoromethyl amines, are scarcely investigated to date. This might be a consequence of the lack of safe, general and high-yielding methodology to access these compounds as well as encountered difficulties in their purifications (see Figure 1).[3] The latest advances in the methodological repertoire include the direct *N*-trifluoromethylation of certain amines, nitriles and azoles with electrophilic[4] or radical-based reagents,[5] posing continued challenges in terms of generality and late-stage synthetic applications to compounds with incompatible additional functionality. Alternatively, N-CF_3 compounds can be made in a two-step sequence from free amines via oxidative transformations of dithiocarbamates.[6] Access to the latter can be non-trivial however with respect to functional group compatibility, as their syntheses generally require strong base, alkylating or toxic reagents.[7]

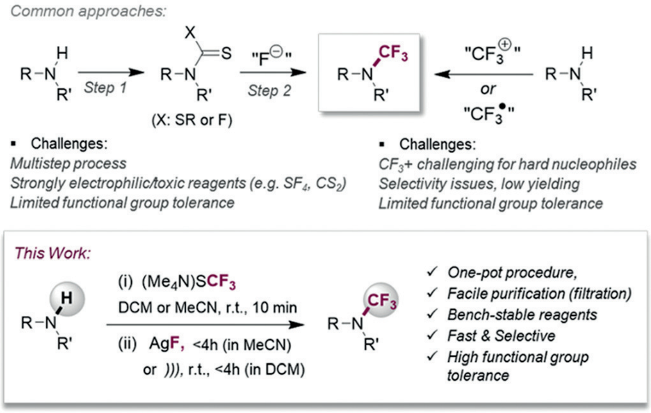

Figure 1. Overview of methods to access N-CF_3 compounds and this work.

A mild, safe and operational simple synthetic route to N-CF_3 compounds would hence be desirable and may enable numerous avenues in chemical and biomedical research. For example, the frequently encountered facile oxidation of amines in metabolic processes should be less pronounced under N-CF_3 modification.[8] In addition, our calculations of selected drug molecules indicate similar conformational preferences but increased log*P* values for N-CF_3 vs. N-Me.[9] Moreover, a promising isolated study found the N-CF_3 analogue of floxacin to retain similar antibacterial activities as its methylated counterpart.[10]

We herein demonstrate the rapid and selective formation of a wide range of trifluoromethylated amines from secondary amines. The high-yielding, one-pot strategy is based on a polarity inversion and in situ formation of a thiocarbamoyl fluoride intermediate using the bench-stable $(Me_4N)SCF_3$ reagent.

As part of our ongoing mechanistic and methodological program[11] that also focusses on the generation of fluorine-containing compounds,[12] we recently developed metal-catalyzed C–SCF_3 bond formation protocols of aryl (pseudo)-halides, using the bench-stable "SCF_3^-" source $(Me_4N)SCF_3$.[13,14] During these investigations, we encountered the unexpected formation of a challenging class of compounds, that is, a thiocarbamoyl fluoride. The subjection of one equivalent of $(Me_4N)SCF_3$ to *N*-methylaniline in toluene at room temperature remarkably gave rise to facile and quantitative formation of *N*-methyl-*N*-phenylthiocarbamoyl fluoride **1a** within minutes without any need for additional reagents or catalysts (see Scheme 1). Although thiocarbamoyl chlorides are well known and widely reported, interestingly, the fluoride equivalent has seen much less precedence.[15] The few reported syntheses relied on the use of

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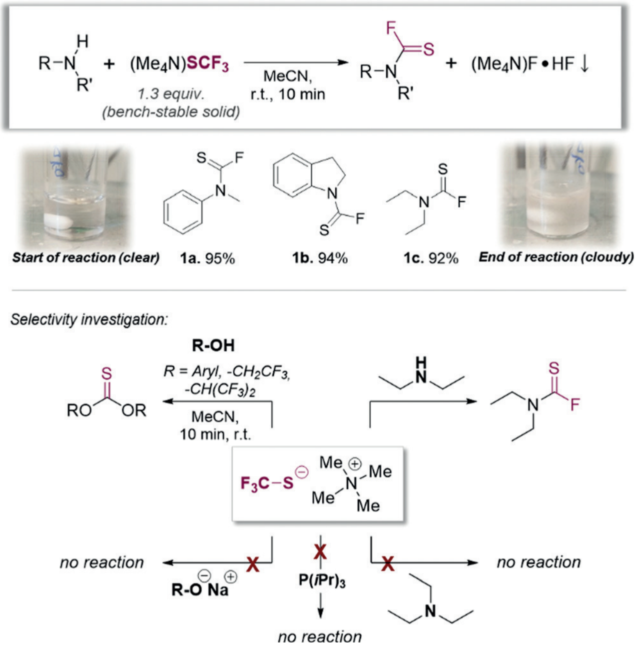


Scheme 1. Generation of thiocarbamoyl fluorides via umpolung (top) and selectivity in reactivities with alternative nucleophiles (bottom).

highly toxic and strongly electrophilic reagents.[16] As such, our discovery constitutes a considerable advance, being safe, convenient, rapid and utilizing a bench-stable solid as the sole reaction partner for quantitative transformation within minutes. To test the generality, we explored a variety of additional secondary amines for their reactivities with $(Me_4N)SCF_3$. Scheme 1 shows two additional examples of isolated thiocarbamoyl fluorides (and Tables 1 and 2 report their follow-up usage). Notably, through the addition of hexane after 10 min reaction time, all side-products are precipitated, allowing facile isolation of the thiocarbamoyl fluoride upon filtration, if desired.

Given this intriguing and non-obvious reactivity of two nucleophiles (R_2NH and CF_3S^-) to generate the highly electrophilic thiocarbamoyl fluoride quantitatively, we set out to explore this transformation in greater detail. On first sight, a reasonable scenario would appear to be the in situ generation of $F_2C{=}S$ upon fluoride elimination,[17] which could then serve as an electrophile to the amine. However, dissolved $(Me_4N)SCF_3$ salt in MeCN neither generated $F_2C{=}S$ by itself nor under the addition of a small amount of water.[18] Furthermore, if generated $F_2C{=}S$ were to trigger the observed reactivity, we would also expect to see transformation with nucleophiles other than secondary amines. However, subjection of the $(Me_4N)SCF_3$ reagent to tertiary amines or phosphines did not give rise to any reaction,[19] indicating potential for selectivity which would otherwise not be given with standard electrophiles that would preferentially select for the most nucleophilic site (Scheme 1). In our case, selectivity for the "heteroatom-H" site appears to be given.

We next investigated oxygen-based nucleophiles.[17b] We observed that the reaction of phenol with $(Me_4N)SCF_3$ gives rapid formation of the thiocarbonate species ROC(S)OR within minutes. Similarly, also rather weakly nucleophilic alcohols, such as 2,2,2-trifluoroethanol ($N = 1.11$ according to Mayr's scale[20]) or hexafluoroisopropanol ($N = -1.93$) formed the corresponding thiocarbonates upon subjection to $(Me_4N)SCF_3$. On the other hand, the arguably more nucleophilic 4-(trifluoromethyl)phenoxide did not markedly react with $(Me_4N)SCF_3$, showing only traces of product over the course of 15 h at room temperature (see Scheme 1, bottom).

These results clearly indicate that in contrast to established transformations to access these and related compound classes, the nucleophilicity of the to be functionalized heteroatom is not the decisive reactivity factor, therefore offering a platform for distinct selectivities and functional group tolerance in the context of late-stage applications of this methodology.

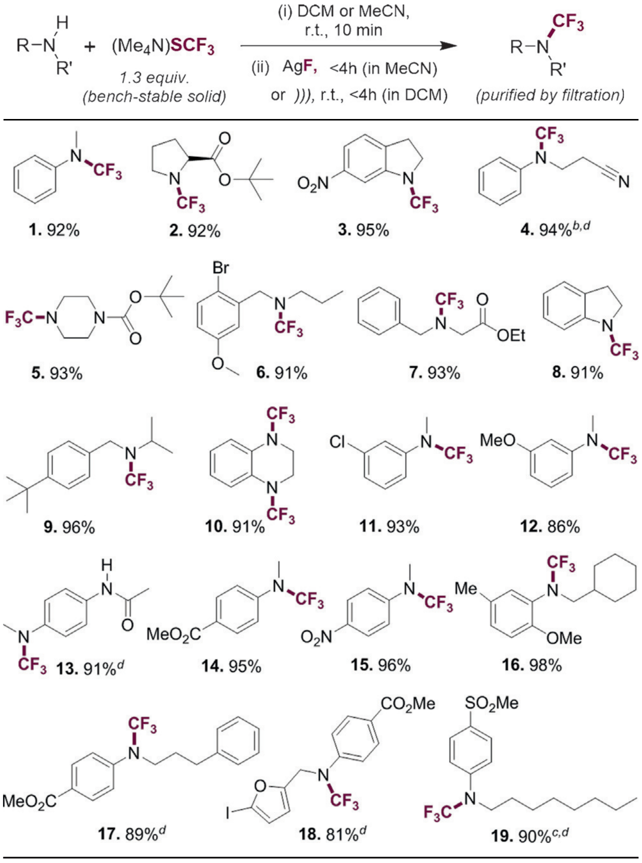
That said, we next set out to further transform this valuable intermediate to trifluoromethyl amines. We anticipated that the distinct selectivity imposed in the first reaction step should ultimately translate to the final N-CF_3 compounds.

Building on Tyrra's report that described the AgF-mediated conversion of a diethylcarbamoyl fluoride to N-CF_3,[21] we subsequently investigated the feasibility of this protocol to convert a wider range of thiocarbamoyl fluorides, including those generated in situ under our conditions. Mixing *N*-methylaniline in acetonitrile with $(Me_4N)SCF_3$ led to the quantitative formation of the corresponding thiocarbamoyl fluoride within 10 minutes at room temperature, as judged by quantitative ^{19}F-NMR analysis of the reaction mixture. Subsequent direct addition of AgF (3 equiv) to the same mixture gave complete conversion to the corresponding trifluoromethylated amine **1** in Table 1 within two hours. The reaction between AgF and the thiocarbamoyl fluoride was found to proceed smoothly at room temperature or higher temperature (50 °C).[22] No side-products, for example, arising from a Ritter-type reaction as commonly observed under electrophilic trifluoromethylation of amines,[4b] were detected.

Notably, the only by-products generated in this one-pot two-step sequence are salts [$(Me_4N)HF_2$ and Ag_2S]. Those can readily be precipitated from the reaction mixture via the addition of low polarity solvents, such as hexane or pentane, leaving the desired N-CF_3 target compound as the only product dissolved in the organic phase (MeCN). Thus, only filtration and solvent removal are required to isolate the desired N-CF_3 compounds. For more volatile products, we identified that it is also possible to use the lower boiling solvent CH_2Cl_2 as reaction medium. Although AgF is not soluble in CH_2Cl_2, sonication of the reaction mixture mitigates this and the trifluoromethylamines are generated equally effectively.

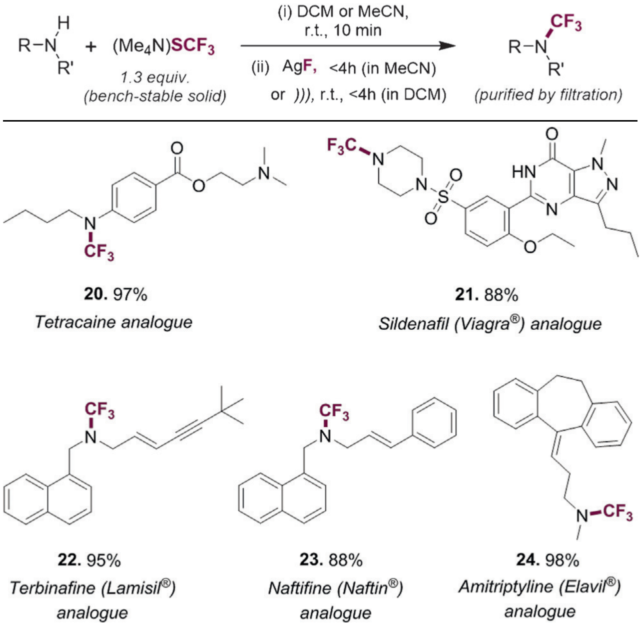
This one-pot protocol therefore presents a convenient, safe and high-yielding route to trifluoromethylamines, and we subsequently set out to investigate its full potential. Table 1 presents an overview of the studied amines. We found our protocol to be compatible with aromatic as well as aliphatic secondary amines, generating the corresponding N-CF_3 products in excellent yields (98–81 %). Electron-poor and rich amines were coupled with the same efficiency (see Table 1). Exclusive selectivity for the NH site and a high

Table 1: Scope of trifluoromethylation of secondary amines.[a]



[a] Reaction conditions: Amine (0.2 mmol), $(Me_4N)SCF_3$ (46 mg, 0.26 mmol), AgF (76 mg, 0.6 mmol) solvent (1.5 mL). [b] Formation of thiocarbamoyl fluoride in 1 h. [c] Formation of thiocarbamoyl fluoride in 24 h. [d] Filtration and column chromatography performed.

Table 2: *N*-Trifluoromethylation of important drug molecules.[a]



[a] Reaction conditions: Amine (0.2 mmol), $(Me_4N)SCF_3$ (46 mg, 0.26 mmol), AgF (76 mg, 0.6 mmol) solvent (1.5 mL).

functional group tolerance were observed. Halogens (**6**, **11**, **18**), ester (**2**, **5**, **7**, **14**, **17**), nitrile (**4**), nitro (**3**, **15**), amide (**13**), sulfonyl (**19**), methoxy (**12**, **16**) as well as a heterocycle (**18**) were all tolerated. Two protected amino acids, that is, the glycine (**7**) and proline (**2**) derivatives, were also successfully synthesized. As such, the presented methodology constitutes a significant improvement to previous protocols in terms of operational simplicity and generality.

As a further test of our newly developed methodology for pharmaceutical and agrochemical applications, we next investigated nitrogen-containing drug molecules of greater complexity. We successfully *N*-trifluoromethylated tetracaine **20**, a widely used anesthetic, in 97% yield (Table 2).[23] Similarly, there are numerous N-Me containing drugs on the market, and we therefore also investigated the feasibility to synthesize their N-CF_3 bioisosteres.[24] In this context, we primarily focused on pharmaceuticals that are listed on the "WHO Model List of Essential Medicines" (a list containing the most important medications required in any basic health system).[25] We prepared the N-CF_3 analogue of Sildenafil **21** in high yield (88%), the most widely used drug against erectile dysfunction (Viagra®),[26] the antifungal agents terbinafine **22** (in 95%),[27] and naftifine **23** (88%) as well as amitriptyline **24** (98%)[28] that finds use in the treatment of mental illnesses (see Table 2). We were pleased to obtain high yields in all cases, demonstrating the scope and applicability of this protocol in a pharmaceutical context, as heterocycles, tertiary amines, alkynes and alkenes were well tolerated.

In summary, we reported a convenient, safe and operationally simple one-pot protocol for the rapid and mild trifluoromethylation of secondary amines. The readily accessible bench-stable $(Me_4N)SCF_3$ salt formally serves as CF_3 source via initial reaction between the SCF_3-anion and the amine. Upon umpolung a rarely encountered and valuable thiocarbamoyl fluoride intermediate is generated quantitatively in situ that can subsequently be converted to the corresponding N-CF_3 compounds upon reaction with AgF. The purification consists solely of precipitation of the salt by-products with non-polar solvent, followed by filtration. The umpolung strategy allowed distinct selectivities in trifluoromethylation which is not governed by nucleophilicity, but instead by the availability of an "N-H" unit. As such, the protocol displays a wide functional group tolerance, and was demonstrated to be compatible with carbonyl, alkene, alkyne, tertiary amine, nitrile, nitro, heterocycles as well as protected amino acids and relevant pharmaceuticals.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: amines · synthetic methods · thiocarbamoyl fluoride · trifluoromethylation

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