Synthetic Methods

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N-Trifluoromethylthiosaccharin: An Easily Accessible, Shelf-Stable, Broadly Applicable Trifluoromethylthiolating Reagent**

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Abstract: *A new, electrophilic trifluoromethylthiolating reagent, N-trifluoromethylthiosaccharin, was developed and can be synthesized in two steps from saccharin within 30 minutes. N-trifluoromethylthiosaccharin is a powerful trifluoromethylthiolating reagent and allows the trifluoromethylthiolation of a variety of nucleophiles such as alcohols, amines, thiols, electron-rich arenes, aldehydes, ketones, acyclic β-ketoesters, and alkynes under mild reaction conditions.*

As one of the most lipophilic structural moieties, the trifluoromethylthio group (CF_3S) has attracted special interests from both academia and the pharmaceutical industry.[1] Incorporation of the trifluoromethylthio group into leading drug candidates has become an indispensible strategy for drug discovery, thus resulting in a growing demand which challenges chemists to provide reliable methods for the introduction of this highly valued structural component.[2,3]

One general strategy for the formation of trifluoromethylthiolated compounds is the trifluoromethylation of thiols and their derivatives, and significant progress has been achieved previously.[2] An alternate attractive and straightforward route for the incorporation of the CF_3S moiety is the direct introduction of this functional group at the late stage of a multistep synthetic sequence by employing an easily available yet stable CF_3S reagent.[2i] This strategy is particularly important for those nonspecialized laboratories since it does not require specific skills and use of protective clothing and/or equipment. However, until recently, the choice of electrophilic trifluoromethylthiolating reagents was undeniably limited and their access relatively difficult.

The first and simplest electrophilic trifluoromethylthiolating reagent was trifluoromethylsulfenyl chloride (CF_3SCl).[4] Although it reacts with a variety of nucleophiles, the gaseous and toxic nature of the reagent restricts its further utilization.[5] *N*-Trifluoromethylthiophthalimide (**1**; Figure 1),[6] which was originally prepared from phthalimide and CF_3SCl, now can be accessed by reactions of *N*-chloro- or *N*-bromophthalimide with $CuSCF_3$ or $AgSCF_3$.[6d,e] Nevertheless, its synthetic applications are rather limited. Since 2008, three different electrophilic trifluoromethylthiolating reagents emerged as a potentially valuable replacement to CF_3SCl. Billard and co-workers reported the preparation of the trifluoromethanesulfanylamides **2** from DAST, CF_3SiMe_3, and primary amines. As one of the leading trifluoromethylthiolating reagents, **2** is effective for trifluoromethylthiolation of alkenes, alkynes, amines, indoles, and Grignard or lithium reagents,[7] although a strong Lewis acid or Brønsted acid as activator is generally required. In early 2013, Shen and Lu reported the trifluoromethyl-substituted thioperoxide reagent **3** which could trifluoromethylthiolate a variety of substrates such as aryl and vinyl boronic acids, alkynes, aldehydes, and β-ketoesters.[8] However, the preparation of the reagent requires a multistep sequence. Shortly after, Shibata and co-workers designed and synthesized a new electrophilic trifluoromethylthiolating reagent (**4**), a trifluoromethanesulfonyl hypervalent iodonium ylide, which reacted only with enamines, indoles, and two examples of β-ketoesters, through an in situ reduction process.[9] Thus, development of a readily accessible, easy-to-handle, electrophilic trifluoromethylthiolating reagent, which is effective for a broad substrate scope under relatively mild reaction conditions, is highly desirable.

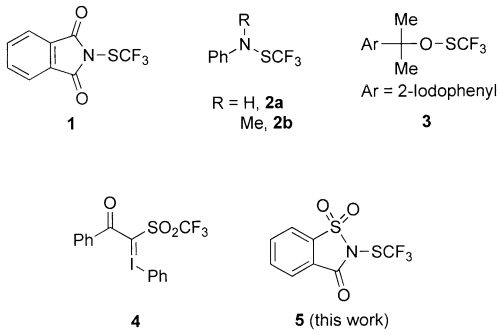

Figure 1. Electrophilic trifluoromethylthiolating reagents.

Herein, we report the design and synthesis of the *N*-trifluoromethylthiosaccharin (**5**), which can be efficiently synthesized from commercially available *N*-chlorosaccharin or through a two-step process from saccharin, a readily available, low-cost commodity. The superior reactivity of **5** was further demonstrated by trifluoromethylthiolation a variety of nucleophiles such as alcohols, amines, thiols, and electron-rich arenes, aldehydes, ketones, and acyclic β-ketoesters under mild reaction conditions. The fast rates, broad scope, and tolerance of functionality of these trifluoromethylthiolation reactions made **5** very attractive as a general

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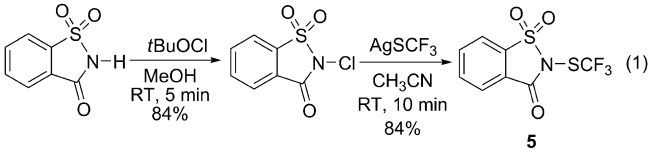
reagent which will allow rapid incorporation of CF_3S into small molecules.

N-trifluoromethylthiosaccharin (**5**) is easily synthesized from the reaction of *N*-chlorosaccharin with $AgSCF_3$ in CH_3CN for 10 minutes at room temperature, and is isolated in 84% yield. Alternatively, it could be prepared by a two-step procedure, as shown in Equation (1). Treatment of saccharin



(1)

with *tert*-butyl hypochlorite in methanol at room temperature for 5 minutes generates *N*-chlorosaccharin,[10] which was then reacted with $AgSCF_3$ in CH_3CN for 10 minutes to form **5** in 86% yield, as determined by ^{19}F NMR spectroscopy. The reaction can be easily scaled up to 6.0 grams and **5** was isolated as a white solid in 84% yield. The compound **5** was characterized by ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy and elemental analysis. The structure of **5** was unambiguously confirmed by single-crystal X-ray analysis (see the Supporting Information for details).[17]

The compound **5** is a highly stable, crystalline compound. No detectable decomposition was observed after storage for more than one month at ambient temperature. It is stable in solvents such as CH_2Cl_2, $ClCH_2CH_2Cl$, toluene, and CH_3CN at room temperature for at least 12 hours as determined by ^{19}F NMR spectroscopy, and is less stable in THF as roughly 60% of **5** was converted into CF_3S-SCF_3 after 48 hours at room temperature. The compound **5** is not stable in more polar solvents such as DMF and DMSO. It was completely decomposed after 5 minutes in DMSO and after 10 hours in DMF at room temperature as determined by ^{19}F NMR spectroscopy.

With this new reagent in hand, we then explored the reactivity of **5** with a variety of nucleophiles. Reaction of 2-(naphthalen-2-yl)ethanol with **5** in the presence of 2.3 equivalents of triethylamine gave a quantitative yield of the CF_3-substituted thioperoxide[11] after 5 minutes at room temperature (Figure 2). In contrast, when **1** was employed, only 12% yield of product was detected and no improvement was observed with elongated reaction time (12 h). Three other reagents, **2**–**4**, which have shown to be active for electrophilic trifluoromethylthiolation for various substrates, each gave less than 2% of the desired product. These results show that **5** displays remarkably increased reactivity compared to other trifluoromethylthiolating reagents. The increased reactivity of **5** compared to that of its analogue **1**, is likely due to the stronger electron-withdrawing property of the sulfonyl group as compared to that of a carbonyl group.

As shown in Scheme 1, **5** could trifluoromethylthiolate a variety of alcohols. Primary, secondary, and tertiary alcohols were readily converted into trifluoromethyl-substituted thioperoxides in excellent yields within 5 minutes. Functional groups such as esters, ketones, halides, and alkenes were

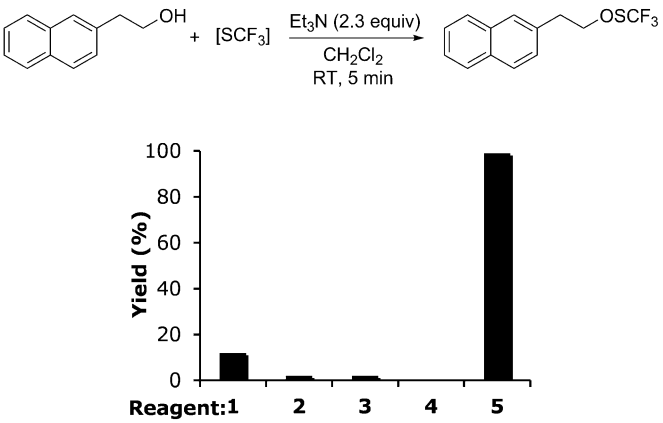
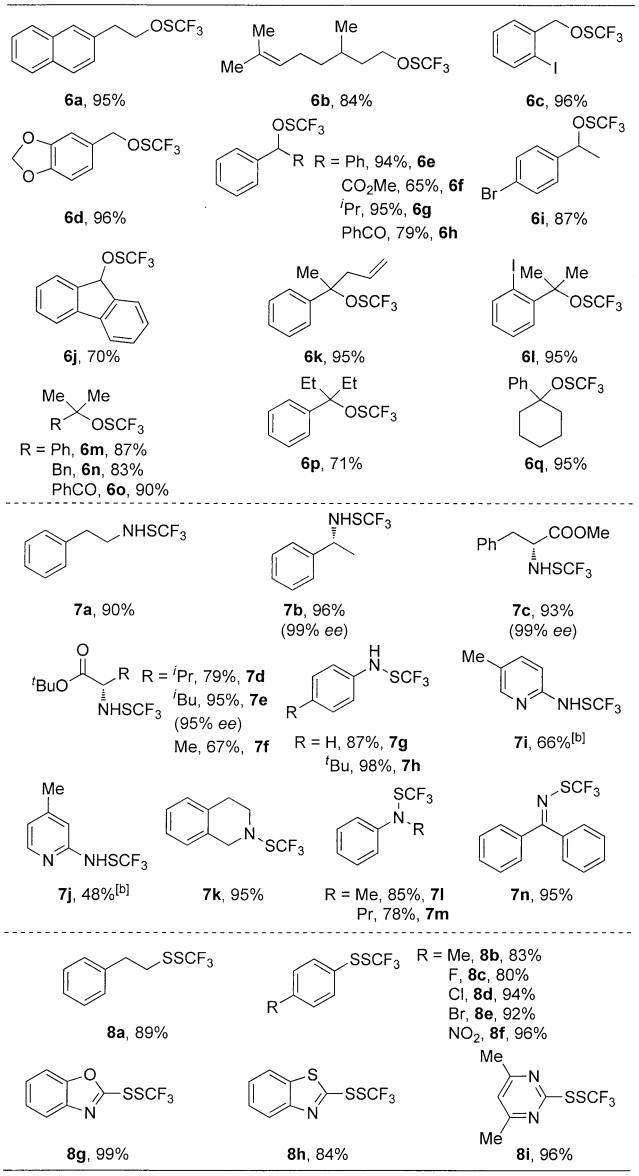


Figure 2. Results observed for reaction of 2-(naphthalen-2-yl)ethanol with the reagents **1**–**5**.

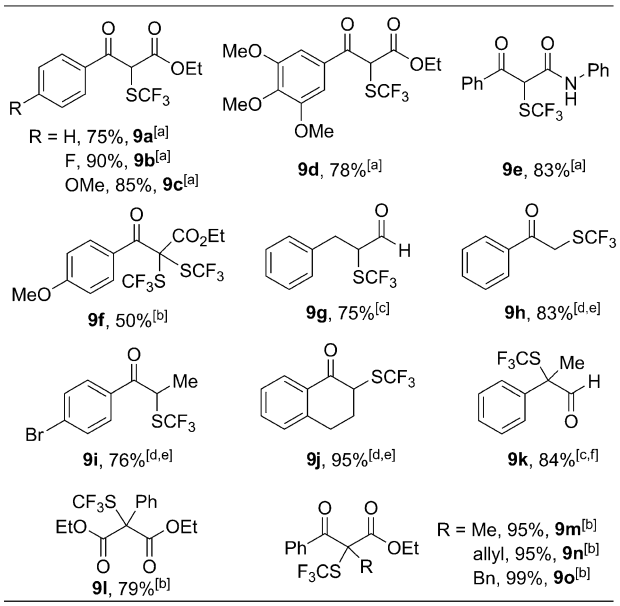
tolerated under standard reaction conditions (**6b**–**c**, **6f**, **6h**–**i**, **6k**–**l**, **6o**). Notably, **6l**, which was previously developed in our group as a trifluoromethylthiolating reagent (reagent **3** in Figure 1) in moderate yields by a multistep synthesis, can now be obtained in 95% in one step within 5 minutes.[8a] The structure of **3** was recently established as a trifluoromethyl-substituted thioperoxide by Buchwald and co-workers through a combination of spectroscopic techniques, derivatization experiments, and the crystal sponge method.[8b]

Not only alcohols but also amines could be expediently trifluoromethylthiolated under mild reaction conditions.[7a,j,12] Reactions of various primary or secondary alkyl amines and arylamines with **5** proceeded in high yields after 1 hour at room temperature (Scheme 1). Billard's reagents **7g** and **7l** (reagents **2a** and **2b** in Figure 1), could also be accessed from **5** in excellent yields. Optically pure alkylamines including α-aminoesters were readily converted into the trifluoromethylthiolated amines in excellent yields without erosion of the enantioselectivity (**7b**–**c**, **7e**). Even an imine could be trifluoromethylthiolated in good yield under these reactions conditions (**7n**). The compound **7n** has been previously synthesized from the trifluoromethanesulfenamide **2a** under the basic conditions.[7j] Reactions of hetarylamines, however, were extremely slow. Billard has shown that Lewis acids such as $TiCl_4$, $SnCl_4$, and $ClSiMe_3$ could activate **2** for trifluoromethylthiolation of olefins.[7b] Inspired by these results, we found that when Me_3SiCl was used as an activator, the reaction of hetarylamines with **5** occurred in acceptable yields of the desired products after 8 hours at 60°C (**7i**–**j**). Previously reported methods for the preparation of trifluoromethylthiolated amines required either the use of DAST,[7a] CF_3SCl, or the presence of 1.1 equivalents of *n*BuLi as the base.[7j]

Encouraged by the superior performance of **5** compared to that of other trifluoromethylthiolating reagents, we further studied the reaction of thiols with **5**. Reactions of **5** with a variety of aryl and heteroaryl thiols occurred in excellent yields. Common functional groups such as fluoride, chloride, bromide, and nitro were tolerated under the optimized reaction conditions (Scheme 1; **8c**–**f**). Alkylthiol also reacted with **5** to provide the desired product in good yield (**8a**). A



Scheme 1. Trifluoromethylthiolation of alcohols, amines, and thiols with **5** under mild reaction conditions. Yields are those of the isolated products. Reaction conditions for alcohols: alcohol (0.3 mmol), **5** (0.39 mmol), Et_3N (100 μL, 2.3 equiv), CH_2Cl_2 (6.0 mL), room temperature 5 min. Reaction conditions for amines: amine (0.30 mmol), **5** (0.30-0.39 mmol), CH_2Cl_2 (6 mL), room temperature, 0.5–1 h. Reaction conditions for thiols: thiol (0.3 mmol), **5** (0.30–0.39 mmol), CH_2Cl_2 (6.0 mL), room temperature, 1 h. [a] Me_3SiCl (1.3 equiv) was added as additive, $ClCH_2CH_2Cl$ was used as solvent, 60 °C for 8 h.

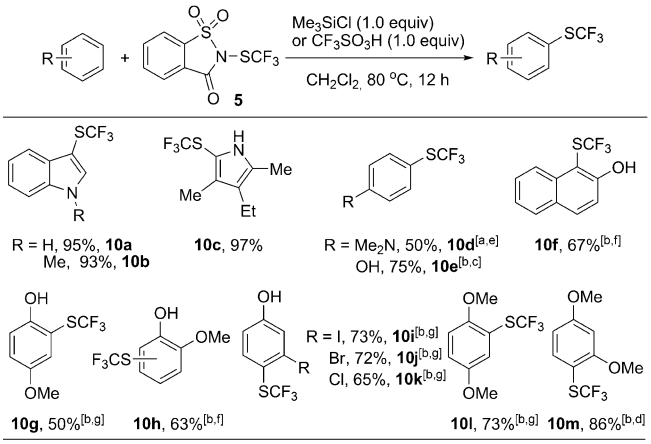


Scheme 2. Trifluoromethylthiolation of β-keto esters, aldehydes and ketones with **5** under mild reaction conditions. Yields are those of the isolated products. [a] Reaction conditions: β-keto ester (0.3 mmol), NaH (0.33 mmol), **5** (0.39 mmol), THF (2.0 mL), 0 °C, 30 min. [b] Reaction conditions: β-keto ester (0.3 mmol), **5** (0.66 mmol), DMAP (1.26 mmol), toluene (6.0 mL), room temperature, 8 h. [c] Reaction conditions: Aldehyde (0.3 mmol), **5** (0.36 mmol), morpholine hydrochloride (30 mol%), CH_2Cl_2 (6.0 mL), 30 °C, 12 h. [d] Reaction conditions: Ketone (0.3 mmol), **5** (0.45 mmol), morpholine hydrochloride (30 mol%), CH_3CN (6.0 mL), 80 °C, 12 h. [e] Me_3SiCl (0.45 mmol) was added. [f] 60 °C, 12 h.

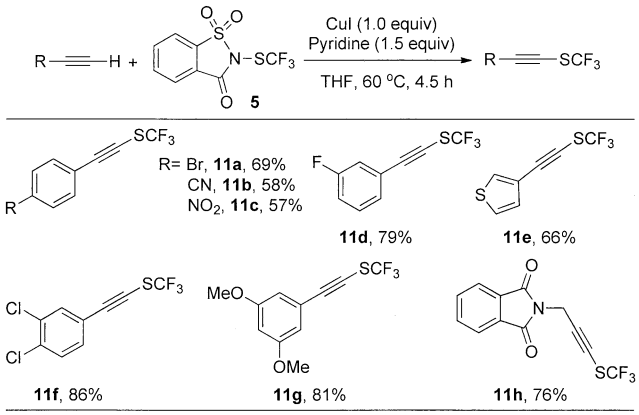
previously known method for the preparation of aryl trifluoromethyldisulfide involved the use of highly toxic CF_3SCl or CF_3SSCF_3.[13] Thus, this method provided a straightforward route for the preparation of a family of potentially useful trifluoromethyl-substituted disulfides.

The incorporation of a CF_3S moiety through the mono-trifluoromethylthiolation of acyclic β-keto esters using trifluoromethylthiolating reagents other than CF_3SCl is quite challenging.[14] The reaction of acyclic β-keto esters with **3** in the presence of 4-dimethylaminopyridine (DMAP) as a base results in a complex mixture.[8a] One example of mono-trifluoromethylthiolation of acyclic β-keto esters was reported recently by Shibata and co-workers. However, the reaction occurred only in 48% yield.[9] It was found that reactions of acyclic β-keto esters with **5** occurred to afford the mono-trifluoromethylthiolated β-keto esters after 0.5 hours at 0 °C when NaH was used as the base (Scheme 2; **9a–d**). Likewise, acyclic β-ketoamide also underwent mono-trifluoromethylthiolation in good yield (**9e**). Interestingly, a ditrifluoromethylthiolated β-keto ester was formed when DMAP was used as the base (**9f**). Reactions of α-substituted acyclic β-keto esters or malonates with **5** occurred smoothly at room temperature to give the trifluoromethylthiolated products in excellent yields (**9l–o**). Reactions of aldehydes and ketones were much less effective when the reactions were conducted using NaH as the base. Only 23% yield of the corresponding trifluoromethylthiolated aldehyde was observed for reaction of 2-phenylpropanal using DMAP as the base. Interestingly, reactions of aldehydes and ketones with **5** generated monotrifluoromethylthiolated products when morpholine hydrochloride was use as the catalyst (**9g–k**).

Since **5** was effective for trifluoromethylthiolation of different nucleophiles, we next evaluated the direct electrophilic trifluoromethylthiolation of arenes.[7c,13c,15] As shown in Scheme 3, a variety of electron-rich arenes reacted with **5** to



Scheme 3. Trifluoromethylthiolation of electron-rich arenes with **5** [a] Reaction conditions: arene (0.3 mmol), **5** (0.36–0.45 mmol), Me_3SiCl (36 μL, 0.30 mmol), CH_2Cl_2 (6.0 mL), room temperature, 30 min. Yields are those of the isolated products. [b] CF_3SO_3H (24 μL, 0.30 mmol) was added as additive instead of Me_3SiCl. [c] 60 °C for 8 h. [d] Room temperature, 4 h. [e] **5** (0.45 mmol), Me_3SiCl (54 μL, 0.45 mmol), CH_3CN (6.0 mL), 60 °C, 18 h. [f] 80 °C, 18 h. [g] 80 °C, 36 h.



Scheme 4. Copper-mediated trifluoromethylthiolation of alkynes. Reaction conditions: alkyne (0.6 mmol), **5** (0.30 mmol), CuI (0.60 mmol), pyridine (72 μL, 0.90 mmol), THF (2.0 mL), 60 °C, 4.5 h. Yields are those of the isolated products.

give the corresponding trifluoromethylthiolated products in good to excellent yields when either Me_3SiCl or triflic acid was used as an activator. For example, reactions of phenol and *N*,*N*-dimethylaniline gave exclusively the *para*-trifluoromethylthiolated products in good yields (**10d**,**e**). Similarly, reaction of 2-naphthanol produced 1-trifluoromethylthiolated-2-naphthanol in 67% yield. Notably, 3-chloro, 3-bromo-, and 3-iodophenol were also converted effectively into trifluoromethylthio-substituted arenes in reasonable yields (**10i–k**). These compounds are of interest since many transition metal catalyzed cross-coupling reactions have been reported, thus allowing additional functional-group transformations.[16]

To further extend the synthetic utility of **5**, we studied the trifluoromethylthiolation of alkynes. After a quick screening of the reaction conditions, it was found that reaction of 1-ethynyl-3-fluorobenzene with **5**, conducted with a combination of 2.0 equivalents of CuI and 3.0 equivalents of pyridine as the catalyst in THF, resulted in full conversion into the trifluoromethylthiolated alkyne in 79% yield. A variety of the terminal alkynes with functional groups such as nitro, cyano, fluoride, chloride, bromide, and amide can be transformed into their corresponding alkynyl trifluoromethyl sulfides in good yields (Scheme 4; **11a–d**, **11f**, **11h**). The reaction conditions for the trifluoromethylthiolation of alkynes were not as efficient as those previously reported.[3h,7f–h,8a] Nevertheless, these results demonstrated the broad reaction scope of **5**.

In summary, a new electrophilc *N*-trifluoromethylthiosaccharin (**5**) for direct trifluoromethylthiolation has been developed. The reagent **5** can be efficiently synthesized in two steps and is effective for the direct transfer of the CF_3S group to various substrates such as alcohols, amines, thiols, β-ketoesters, aldehydes, ketones, electron-rich arenes, and alkynes under mild reaction conditions. The ready availability, ease of handling, and high activity makes **5** very attractive as a general electrophilic reagent for the synthesis of a variety of CF_3S-containting molecules. Studies on the expansion of the scope of this reagent are underway and will be reported shortly.

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[18] During the reviewing of the manuscript, Billard and co-workers reported a general method for mono-trifluoromethylthiolation of carbonyl compounds using a new electrophilic trifluoromethylthiolating reagent: *Chem. Eur. J.* **2014**, *20*, DOI: 10.1002/chem.201403409.

