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

Chunfa Xu, Bingqing Ma, and Qilong Shen*  

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 (CF₃S) has attracted special interests from both academia and the pharmaceutical industry. Incorporation of the trifluoromethylthio group into leading drug candidates has become an indispensable 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.  

One general strategy for the formation of trifluoromethylthiolated compounds is the trifluoromethylation of thiols and their derivatives, and significant progress has been achieved previously. An alternate attractive and straightforward route for the incorporation of the CF₃S 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 CF₃S reagent. 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 trifluoromethylsulfonyl chloride (CF₃SOCl). Although it reacts with a variety of nucleophiles, the gaseous and toxic nature of the reagent restricts its further utilization. N-Trifluoromethylthiophthalimide (1; Figure 1), which was originally prepared from phthalimide and CF₃SCl, now can be accessed by reactions of N-chloro- or N-bromophthalimide with CuSCF₃ or AgSCF₃. Nevertheless, its synthetic applications are rather limited. Since 2008, three different electrophilic trifluoromethylthiolating reagents emerged as a potentially valuable replacement to CF₃SOCl. Billard and co-workers reported the preparation of the trifluoromethanesulfanylaminylides 2 from DAST, CF₃SiMe₃, 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, 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. 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. 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.  

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

DOI: 10.1002/anie.201403983

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201403983.
with tert-butyl hypochlorite in methanol at room temperature for 5 minutes generates N-chlorosaccharin[10] which was then reacted with AgSCF₃ in CH₂CN for 10 minutes to form 5 in 86% yield, as determined by ¹⁹F 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 ¹H, ¹³C, and ¹⁹F 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 CH₂Cl₂, CICH₂CH₂Cl, toluene, and CH₃CN at room temperature for at least 12 hours as determined by ¹⁹F NMR spectroscopy, and is less stable in THF as roughly 60% of 5 was converted into CF₃SCF₂ 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 ¹⁹F 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 CF₃-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 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 7c and 7f (reagents 2a and 2b in Figure 1), could also be accessed from 5 in excellent yields. Optically pure alkylamines including iminoesters 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 7a has been previously synthesized from the trifluoromethanesulfenamide 2a under the basic conditions. Reactions of hetarylamines, however, were extremely slow. Billard has shown that Lewis acids such as TiCl₄, SnCl₄, and ClSiMe₃ could activate 2 for trifluoromethylthiolation of olefins.[7m] Inspired by these results, we found that when Me₃SiCl 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[7n] CF₃SCl, or the presence of 1.1 equivalents of nBuLi as the base.[7o]

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
previously known method for the preparation of aryl trifluoromethyltrisulfide involved the use of highly toxic CF₃SCl or CF₃SSCF₃\[13\]. Thus, this method provided a straightforward route for the preparation of a family of potentially useful trifluoromethyl-substituted disulfides.

The incorporation of a CF₃S moiety through the monotrifluoromethylthiolation of acyclic β-keto esters using trifluoromethylthiolating reagents other than CF₃SCl is quite challenging\[14\]. The reaction of acyclic β-keto esters with 5 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 with 5 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 monotrifluoromethylthiolation 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 used as the catalyst (9g–k).

Since 5 was effective for trifluoromethylthiolation of different nucleophiles, we next evaluated the direct electrophilic trifluoromethylthiolation of amines. As shown in Scheme 3, a variety of electron-rich amines reacted with 5 to

**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), Et₃N (100 µL, 2.3 equiv), CH₂Cl₂ (6.0 mL), room temperature 5 min. Reaction conditions for amine: amine (0.30 mmol), 5 (0.30-0.39 mmol), CH₂Cl₂ (6 mL), room temperature, 0.5–1 h. Reaction conditions for thiols: thiol (0.3 mmol), 5 (0.30–0.39 mmol), CH₂Cl₂ (6.0 mL), room temperature, 1 h. [a] Me₃SiCl (1.3 equiv) was added as additive, CI(CH₂)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), 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%), CH₄Cl (6.0 mL), 30°C, 12 h. [d] Reaction conditions: Ketone (0.3 mmol), 5 (0.45 mmol), morpholine hydrochloride (30 mol%), CH₃CN (6.0 mL), 80°C, 12 h. [e] Me₃SiCl (0.45 mmol) was added. [f] 60°C, 12 h.
These are not the final page numbers!

CF3SCI was reported to have an L(l):1 of between 440 and 880 ppm min⁻¹. Chem. Eng. News 1967, 45, 44.


CCDC 994834 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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.
'Sacch'ed out: A new, electrophilic trifluoromethylthiolating reagent, N-trifluoromethylthiosaccharin (1), was developed and can be synthesized in two steps from saccharin within 30 minutes. The reagent 1 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.