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N-Trifluoromethylthiolated Sulfoximines

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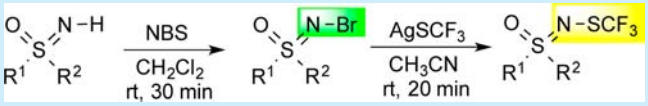
Supporting Information

ABSTRACT: Air- and moisture-stable *N*-trifluoromethylthio sulfoximines have been prepared from *N*−H-sulfoximines via the corresponding *N*−Br derivatives in excellent yields. The two-step process starts with an easy-to-perform bromination at the sulfoximine nitrogen, followed by a reaction with silver trifluoromethanethiolate. A one-pot reaction sequence allows difficult to prepare products to be obtained.



The incorporation of fluoro and fluoroalkyl moieties in organic molecules offers powerful synthetic opportunities for obtaining biologically active compounds.[1] Along these lines, the trifluoromethylthio (SCF_3) group has received particular attention,[2,3] as its presence enhances the lipophilicity of molecules[4] affecting their bioavailability.

Most traditional methods for introducing trifluoromethylthio substituents are characterized by harsh reaction conditions and a pronounced toxicity of the required reagents. In this context, halogen−fluorine exchange reactions, trifluoromethylations of thiols, and the use of gaseous trifluoromethylthiolating agents such as trifluoromethanesulfenyl chloride ($ClSCF_3$), bistrifluoromethyl disulfide (F_3CSSCF_3), or trifluoromethanethiol (F_3CSH) are particularly noteworthy.[2,3] Recent developments have focused on using advanced reagents such as *N*-trifluoromethylthiophthalimide (**1**), *N*-trifluoromethylthio saccharin (**2**), and trifluoromethanesulfanylanilides **3** (Figure 1).[2,5] Furthermore, milder methods employing metal-based reagents and catalysts have been described.[6]

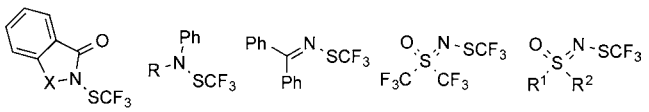


Figure 1. Trifluoromethylthiolating reagents (**1**−**3**) and trifluoromethylthiolated imines (**4**−**6**).

Sulfoximines are monoaza analogs of sulfones,[7] and in contrast to the latter they can chemically be modified at the sulfur fragment by *N*-substitution allowing fine-tuning and adjusting of chemical and physical properties.[8] Recent industrial work illustrates the importance of such structural variability.[9] Fluorinated sulfoximines play a particular role, as they exhibit a broad range of reactivity.[7h,i,10] Derivatives with fluorinated substituents at the sulfoximine nitrogen are particularly scarce with compound **5** being one of the very few examples.[11] In light of the very special substitution patterns of **5** and considering the synthetic challenges in the preparation of this compound (involving a large excess of low-boiling, toxic trifluoromethylsulfenyl chloride) and its isolation (by gas chromatography), we aimed at development of a more general access of *N*-SCF_3-substituted sulfoximines **6**. Here, the realization of this idea is described.

The key to success was the combination of two readily available reagents, *N*-bromo sulfoximines and silver(I) trifluoromethanethiolate (Table 1).[12] The former compounds could easily be prepared in high yields by treatment of the corresponding *N*−H-sulfoximines with *N*-bromo succinimide (NBS).[13] In this manner, for example, compound **8a** was obtained from *N*−H-*S*,*S*-diphenyl sulfoximine (**7a**) in 94% yield after 30 min in DCM at room temperature (Table 1, entry 1).[14] Analogously, *S*-alkyl *S*-aryl sulfoximines **7b**−**l** reacted well affording the respective *N*-brominated products **8b**−**l** in yields ranging from 86% to 99% (Table 1, entries 2−12). Neither steric nor electronic effects of the substituents had an apparent impact on the yield. Attempts to prepare *N*-bromo-*S*-trifluoromethyl-*S*-phenyl sulfoximine (**8m**) and *N*-bromo-*S*,*S*-dimethyl sulfoximine (**8n**) by this protocol remained unsuccessful (Table 1, entries 13 and 14).

For the introduction of the SCF_3 substituent, silver(I) trifluoromethanethiolate was selected, as it is commercially available, easy to handle, and chemically well-studied.[6] Furthermore, the expected formation of insoluble AgBr was envisaged to promote the *N*-trifluoromethylthiolations of the sulfoximines.

To obtain the desired products **6**, the corresponding *N*-bromo sulfoximines **8** were treated with 1.2 equiv of $AgSCF_3$ in acetonitrile. The results of these transformations are summarized in Table 1 (entries 1−12). In general, the yields of the resulting *N*-trifluoromethylthio sulfoximines **6** were high (75−98%) irrespective of the substitution pattern. The only exception was the reaction of *p*-nitro substituted derivative **8e**, which led to **6e** in only 51% yield (Table 1, entry 5). Particularly noteworthy is the good yield in the formation of *S*-cyclopropyl-*S*-phenyl sulfoximine **6b** (Table 1, entry 2) because this substitution pattern occurs in Bayer's kinase inhibitor BAY

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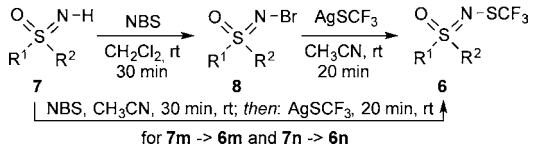
Table 1. *N*-Brominations of *N*−H-Sulfoximines 7 and Subsequent Trifluoromethylthiolations of 8 To Give Products 6[a]



entry	R^1	R^2	yield of **8** (%)	yield of **6** (%)
1	Ph	Ph	94 (**8a**)	85 (**6a**)
2	cyclopropyl	Ph	99 (**8b**)	88 (**6b**)
3	Me	Ph	94 (**8c**)	91 (**6c**)
4	Me	*p*-Br-Ph	99 (**8d**)	80 (**6d**)
5	Me	*p*-NO_2-Ph	99 (**8e**)	51 (**6e**)
6	Me	*p*-MeO-Ph	91 (**8f**)	93 (**6f**)
7	Me	*p*-Me-Ph	94 (**8g**)	75 (**6g**)
8	Me	*p*-Cl-Ph	98 (**8h**)	98 (**6h**)
9	Me	*o*-Br-Ph	94 (**8i**)	86 (**6i**)
10	Me	*o*-MeO-Ph	95 (**8j**)	94 (**6j**)
11	Me	*o*-Cl-Ph	90 (**8k**)	87 (**6k**)
12	Me	*m*-Br-Ph	86 (**8l**)	90 (**6l**)
13[b]	CF_3	Ph	− (**8m**)	55 (**6m**)
14[b]	Me	Me	− (**8n**)	62 (**6n**)

[a]Reaction conditions: (*N*-Brominations) **7** (2.0 mmol) and NBS (2.0 mmol) in CH_2Cl_2 (50 mL) at rt for 30 min; (*N*-Trifluoromethylthiolations) under Ar, **8** (0.5 mmol) in CH_3CN (1 mL), $AgSCF_3$ (0.6 mmol) in CH_3CN (1.5 mL) at rt for 20 min. [b]Use of **7** (0.5 mmol) and NBS (0.5 mmol) in CH_3CN (1.0 mL) at rt for 30 min; then addition of $AgSCF_3$ (0.6 mmol) in CH_3CN (1.5 mL) at rt and stirring for 20 min (both steps under Ar).

1000394.[9a] Furthermore, the high yields of the various halo-substituted *S*-aryl products (Table 1, entries 4, 8, 9, 11, and 12) have to be highlighted because those sulfoximines may serve as starting materials for more densely functionalized derivatives resulting from metal-catalyzed cross-coupling reactions.[15]

Because of the aforementioned inaccessibility of *N*-bromo sulfoximines **8m** and **8n**, an alternative approach toward the respective *N*-trifluoromethylthio derivatives **6m** and **6n** had to be developed. To our delight, those two products could be obtained by a one-pot cascade reaction avoiding the isolation of **8m** and **8n**. Accordingly, NBS was added to a solution of the corresponding *N*−H-sulfoximine in acetonitrile, and a subsequent reaction with $AgSCF_3$ gave **6m** and **6n** in yields of 55% and 62%, respectively (Table 1, entries 13 and 14).

In summary, we prepared novel functionalized sulfoximines with trifluoromethylthio substituents at the sulfoximine nitrogen in high yields. Readily available *N*-bromo derivatives serve as intermediates, which lead to the products upon treatment with $AgSCF_3$. In some cases, a one-pot cascade reaction is advantageous.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization of all products. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01384.

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Notes

The authors declare no competing financial interest.

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