A Practical Approach to *N*-(Trifluoroacetyl)sulfilimines

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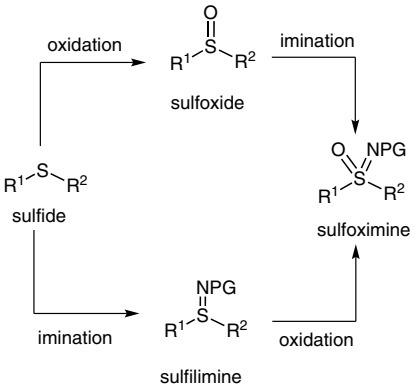
Abstract: A new, simple method for the synthesis of *N*-(trifluoroacetyl)-protected sulfilimines from sulfides by a transition-metal-free, one-pot protocol is presented. The salient features of this process include the use of low-cost 1,3-dibromo-5,5-dimethylhydantoin, mild reaction conditions, and a broad substrate scope. The safety and robustness of the method has also been demonstrated by operations on a kilogram scale. In addition, a chiral resolution of a corresponding sulfoximine was achieved on a large scale.

Key words: *N*-(trifluoroacetyl)sulfilimines, sulfilimines, sulfoximines, chiral resolution

Methods for the preparation of sulfilimines have recently received an increasing level of attention, not least due to the role of sulfilimines as intermediates in the preparation of sulfoximines. The applications of sulfoximines range from chiral ligands[1] in asymmetric catalysis to the design of active ingredients in the life science arena.[2]

The most commonly used synthetic approach to sulfoximines is based on an oxidation–imination protocol commencing from readily available sulfides (Scheme 1). Imination of a sulfoxide is typically accomplished by the use of, for example, sodium azide with sulfuric acid[3] or *O*-mesitylsulfonylhydroxylamine (MSH);[4] however, these reagents are thermally labile and their use for batch operations beyond the laboratory scale is demanding.[5] Accordingly, new imination protocols utilizing (diacetoxyiodo)benzene[6] or electrochemical oxidation[7] have been developed. More recently, catalytic iminations[8] using for example, iron,[9] silver,[10] copper,[11] rhodium,[12] or ruthenium[13] catalysis have been introduced.

Alternatively, the oxidative imination of sulfides to sulfilimines, followed by an oxidation step, can also furnish sulfoximines (Scheme 1). For the sulfilimine synthesis, Bolm's rhodium protocol [$Rh_2(OAc)_4$, MgO, $PhI(OAc)_2$, F_3CCONH_2][12a] and Carreira's method using copper catalysis and lithiated *N*,*O*-bis(trifluoroacetyl)hydroxylamine[14] are noteworthy. Both procedures deliver a broad range of synthetically useful *N*-(trifluoroacetyl)-protected sulfilimines. More recently, a metal-free process was reported by Ochiai, Nakanishi, and coworkers who introduced a sulfonylimino-λ^3-bromane reagent.[15]

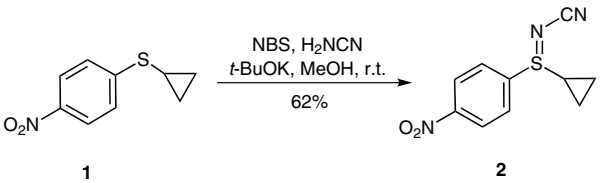


Scheme 1 Synthetic approaches to sulfoximines (PG: protecting group)

When we embarked on this chemistry, we were seeking a transition-metal-free process which makes use of safe, inexpensive reagents and proceeds under mild conditions in one pot, to transfer sulfides into sulfilimines. In particular, we were interested in *N*-(trifluoroacetyl)-protected sulfilimines as the N-protecting group can be easily removed under mild conditions.[12a]

The starting point for our investigations was Bolm's report on the conversion of sulfides into *N*-cyanosulfilimines, which can serve as precursors for sulfoximines, employing cyanogen amine and *N*-bromosuccinimide (NBS) or iodine in the presence of potassium *tert*-butoxide.[16]

Under this protocol, our reference sulfide **1**, which is a key structural element of a drug candidate,[17] was converted smoothly into the *N*-cyanosulfilimine **2** (Scheme 2); however, concomitant formation of the corresponding sulfoxide **4** was observed at a considerable level, which reduced the yield of **2** to 62% on a 0.5 mol scale.



Scheme 2 Initial oxidative imination of sulfide **1**

Subsequently, we replaced cyanogen amine by trifluoroacetamide as the nitrene source under otherwise similar conditions. To our dismay, we obtained sulfoxide **4** as the major product (Table 1, entry 1). We further investigated

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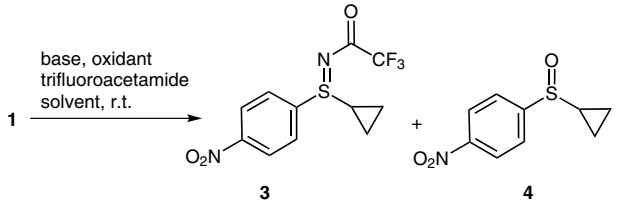
the influence of the reaction components (oxidation agent, base, solvent) on the transformation. To this end, we found that replacement of NBS by the low-cost bromination agent 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) significantly improved the ratio of sulfilimine **3** to sulfoxide **4** (Table 1, entries 3–9). Additionally, the choice of solvent had a dramatic impact on the **3**/**4** ratio. When the DBDMH-promoted conversion was conducted in methanol (Table 1, entry 3), desired **3** and undesired **4** were formed to similar extent, while the use of dichloromethane (Table 1, entry 4) suppressed formation of the sulfoxide **4** almost completely. Furthermore, a variety of bases, such as sodium hydride, cesium carbonate, and potassium *tert*-butoxide are tolerated with DBDMH as oxidation agent to yield a high preference for sulfilimine formation.

Table 1 Imination of Sulfide **1**[a]



Entry	Solvent	Oxidant	Base	Ratio **3**/**4**[b]
1	MeOH	NBS	*t*-BuOK	39:61
2	MeOH	NBS	NaOMe	45:55
3	MeOH	DBDMH	*t*-BuOK	58:42
4	CH_2Cl_2	DBDMH	*t*-BuOK	98:2
5	THF	DBDMH	NaH	97:3
6	MeCN	DBDMH	Cs_2CO_3	87:13
7	MeCN	DBDMH	NaH	98:2
8	MTBE	DBDMH	NaH	97:3
9	1,4-dioxane	DBDMH	*t*-BuOK	83:17

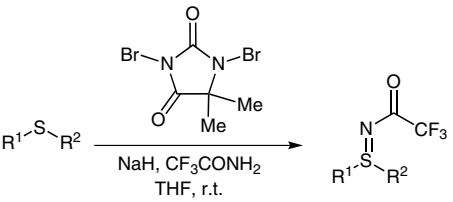
[a] Reaction conditions: sulfide **1** (1 equiv), trifluoroacetamide (1.5 equiv), base (1.5 equiv), oxidant (1.5 equiv), solvent (*c* 0.3 M sulfide), 20 °C.
[b] Ratio derived from the HPLC trace (area%) of the reaction mixture after 3 h.

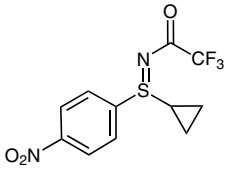
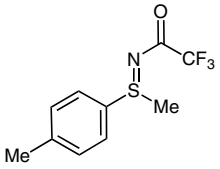
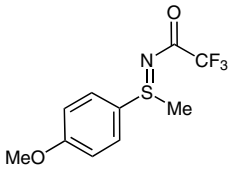
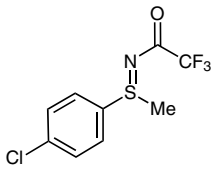
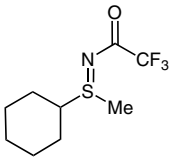
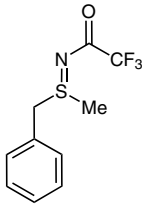
In order to evaluate the scope of this transformation, we selected the conditions listed in Table 1, entry 5 (NaH, THF) for additional studies, due to the good solubility of DBDMH in tetrahydrofuran.[18]

As illustrated in Table 2,[19] a variety of sulfides can be converted into the corresponding *N*-(trifluoroacetyl)-protected sulfilimines. The substrates included aromatic sulfides with a range of electronic properties (Table 2, entries 1–4) and aliphatic sulfides (Table 2, entries 5 and 6), demonstrating the scope of this reaction.

Additionally, we were interested in the robustness of this method. Therefore, we produced several batches of sulfilimine **3** (Table 2, entry 1) on a 7.4 mol scale to give 1.84 kg of sulfilimine per batch, with an average yield of 81%.

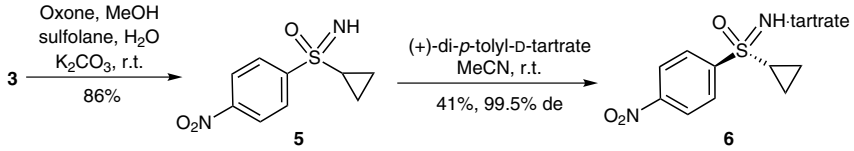
Table 2 Scope of the Sulfide Imination[a,18]



Entry	Sulfilimine product	Yield (%)
1		81
2		88
3		81
4		74
5		77
6		71

[a] Reaction conditions: sulfide (1 equiv), trifluoroacetamide (1.5 equiv), NaH (1.5 equiv), DBDMH (1.5 equiv), THF, 20 °C; see the Supporting Information for product analytical data.

Because unsymmetrically substituted sulfilimines and sulfoximines bear a stereogenic sulfur atom, a stereoselective imination process is highly desirable. To date, the direct asymmetric imination of sulfides remains a challenge,[12b,20] and oxidative imination of optically active



Scheme 3 Synthesis of optically pure sulfoximine **6** (see Supporting Information for experimental details)

sulfoxides under retention of the sulfoxide configuration has been more widely employed.[12a,21]

Especially for larger scale operations, resolution of the sulfoximine racemate via diastereoselective salt formation is a powerful method. For instance, (+)-*S*-methyl-*S*-phenylsulfoximine has been prepared in enantiopure form by resolution with (+)-10-camphorsulfonic acid.[22]

Along these lines, we explored a method to resolve the sulfoximine derived from our lead sulfilimine **3**. Accordingly, **3** was converted into the sulfoximine using potassium peroxymonosulfate (Oxone®)[23] as oxidant, which is available in bulk quantities (Scheme 3). The ternary solvent mixture sulfolane–water–methanol proved beneficial for this protocol, since good solubility of all reaction components was achieved. When the pH was adjusted to pH 10 during the reaction, the oxidation rate was accelerated and the *N*-(trifluoroacetyl)-protecting group was cleaved in one pot to give sulfoximine **5** in 86% yield.

Finally, we found that *rac*-**5** can be resolved by a single crystallization with (+)-di-*p*-tolyl-D-tartrate in acetonitrile to give the corresponding tartrate salt with high optical (99.5% de) and chemical purity in 41% yield. This protocol was performed on an 8.5 mol scale to give 2.1 kg of the tartrate salt per batch.

In conclusion, we have presented a new method for the synthesis of *N*-(trifluoroacetyl)-protected sulfilimines from sulfides by a simple, one-pot transition-metal-free protocol that is also applicable for large-scale operations. The salient features of this process include the use of safe, low-cost, commercially available reagents, mild reaction conditions, and a broad substrate scope. We have also demonstrated that downstream chemistry can lead to optically active sulfoximines by employing a new resolution process with (+)-di-*p*-tolyl-D-tartrate. The scope of this crystallization process will be the subject of further investigations.

Acknowledgment

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Supporting Information for this article, including analytical data for the sulfilimine products in Table 2 and for products **5** and **6**, as well as details for the large-scale procedures, is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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(18) Calorimetric measurements revealed that THF solutions of DBDMH have a limited stability at 20 °C and should therefore be handled at 2–8 °C. Solutions of DBDMH in, for example, 1,4-dioxane are more robust and can be used as an alternative without a detrimental effect on quality or yield.

(19) **General Experimental Procedure for the Formation of *N*-(Trifluoroacetyl)-Protected Sulfilimines on a Laboratory Scale**
In an inert gas atmosphere, a mixture of the sulfide (34.7 mmol) and trifluoroacetamide (5.89 g, 52.1 mmol) in THF (20 mL) was added under ice cooling within 45 min to a suspension of NaH (60% in mineral oil; 1.25 g, 31.3 mmol) in THF (25 mL). Then, a freshly prepared solution of 1,3-dibromo-5,5-dimethylhydantoin (14.9 g, 52.1 mmol) in THF (37 mL) was added within 60 min at 20 °C. The mixture was stirred for 3 h; the reaction was quenched with 10% aq citric acid solution (35 mL), and toluene (70 mL) was added. The organic layer was washed with 25% aq sodium sulfite solution (35 mL) and water (3 × 40 mL). The solvent was removed by distillation, and the residue was purified by silica gel chromatography (EtOAc–*n*-heptane = 1:1).

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