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Strategies for oxidative synthesis of *N*-triflyl sulfoximines†

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The oxidation of various structurally different *N*-trifluoromethylthio sulfoximines was investigated using different oxidizing agents and conditions. Mono- and disubstituted phenyl methyl and phenyl cyclopropyl *N*-trifluoromethylthio sulfoximines were oxidized with NaOCl·5H₂O in water, while sterically hindered substrates bearing bulkier alkyl chains or two phenyl rings required the addition of MeCN to the reaction mixture. Chloro-, bromo-, and cyano-substituted substrates, as well as substrates bearing the benzyl groups, required a completely different approach using *m*-CPBA in DCM. Each method was tested on a gram-scale, with almost no difference in yield or reaction profile. The methods were also tested on *N*-*p*-tolylthio sulfoximine where successful oxidation to the corresponding sulfone derivative was observed. Finally, the *N*-triflyl sulfoximines acquired in the oxidations were examined in terms of stability and reactivity in Suzuki–Miyaura and Sonogashira coupling reactions, as well as many others. The selective mono- and dinitration of 4-methoxyphenyl *N*-triflyl sulfoximine was demonstrated by using nitric and sulfuric acid. *N*-triflyl sulfoximines were found to be stable in concentrated aqueous NaOH and HCl solutions and at elevated temperatures.

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Introduction

The synthesis of sulfoximines and their functionalization continues to be an interesting topic, largely due to the properties that these compounds possess. These versatile molecules have found wide-ranging applications, serving as synthons in pharmaceutical and medicinal chemistry,^{1–6} in agrochemistry,^{7–9} as chiral auxiliaries,^{10,11} and more.^{12,13}

This article focuses on the functionalization and modification of groups on the nitrogen atom of the sulfoximine group. Recent examples of N–C type functionalizations include the procedures for the synthesis of *N*-allyl sulfoximines using allylic alcohols in a cocatalytic organoboron/Pd process¹⁴ and *N*-aryl sulfoximines using an inexpensive copper catalyst.¹⁵ Alkylation of sulfoximines could be achieved with an operationally simple Mitsunobu-type reaction using alcohols¹⁶ or by a copper-catalyzed photochemical reaction with diacyl peroxides.¹⁷ NH-sulfoximines can also be functionalized *via* an epoxide ring opening assisted by a catalytic amount of calcium(II) triflimide to afford 1,2-sulfoximidoyl ethanols.¹⁸ Decarboxylative sulfoximination of benzoic acids,¹⁹ oxidative decarboxylative sulfoximination of cinnamic acids,²⁰ C–H sulfoximination of arenes²¹ and aerobic acylation with methylarenes led to *N*-functionalized sulfoximines.²² *N*-sulfenyl sulfoximines (=N–S–R) can be

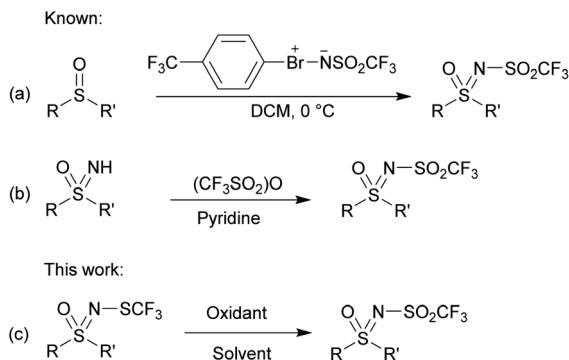
obtained from sulfoximines and various sulfur sources, *i.e.*, thiosulfonates and NaH,²³ thiols and I₂/H₂O₂ in PEG 400,²⁴ or from disulfides under mechanochemical²⁵ and electrochemical conditions.^{26–28} Regioselective chloro-sulfoximidations of allenes under solvent-free mechanochemical²⁹ and photochemical³⁰ conditions also gave *S*-substituted sulfoximines.

N-sulfonylsulfoximines (=N–SO₂–R), which are similar to the compounds studied in this paper, have already been reported in the literature. The two main approaches to synthesize these compounds are based on the oxidation of *N*-sulfonyl sulfilimines and the transfer of the –NSO₂– functionality to sulfoxides. The oxidation of *N*-sulfonyl sulfilimines with oxidizing agent/ruthenium tetroxide effectively gave the corresponding *N*-sulfonyl sulfoximines.^{31,32} Further oxidations of various sulfilimines were carried out with different oxidizing agents, *e.g.*, *m*-CPBA (*m*-chloroperoxybenzoic acid),³³ NaOCl/Bu₄NBr,³⁴ and electro generated peroxodicarbonate.³⁵ The reaction of sulfoxide and tosyl azide in the presence of copper resulted in the formation of *N*-benzenesulfonyldimethyl sulfoximine in 97% yield.³⁶ The imination of sulfoxides with various sulfonamides catalyzed by silver(I),³⁷ copper(II),³⁸ copper(I),³⁹ rhodium(II),⁴⁰ iron(III)⁴¹ and uncatalyzed imination of sulfoxides are also known.⁴² Iminoiodanes can be used as imination agents for sulfoxides.⁴³ Sodium alkyl- and aryl-sulfinates with catalytic amounts of I₂ and H₂O₂ in water undergo oxidative coupling to form *N*-sulfonyl-protected sulfoximines in good yields.⁴⁴ Another mild *N*-sulfonylation of NH-sulfoximines was demonstrated using aryldiazonium tetrafluoroborates, 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) (DABSO) and a cheap copper catalyst.⁴⁵

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† Electronic supplementary information (ESI) available: Full experimental detail, copies of ¹H, ¹⁹F and ¹³C NMR spectra. See DOI: <https://doi.org/10.1039/d4ra04992f>





Scheme 1 Previous and current work.

The synthetic routes described in the literature for the preparation of *N*-triflyl sulfoximines are rather limited and are based on the transfer of $-\text{NSO}_2\text{CF}_3$ and $-\text{SO}_2\text{CF}_3$ moieties. By using sulfonylimino- λ^3 -bromane under mild conditions, the sulfonylimino group was transferred to sulfides and sulfoxides yielding *N*-triflyl sulfilimines and sulfoximines, respectively (Scheme 1a).⁴⁶ The other approach is based on the functionalization of sulfoximines using trifluoromethanesulfonic anhydride and pyridine as a base (Scheme 1b).⁴⁷

N-trifluoromethylthiolated sulfonimidamides and sulfoximines possess various biological activities,⁴⁸ and we reasoned that their oxidized $=\text{NSO}_2\text{CF}_3$ derivatives might also be interesting in this regard. Our aim was threefold: to explore the oxidation of *N*-trifluoromethylthio sulfoximines to the corresponding *N*-sulfonyl sulfoximines, to propose an alternative oxidative pathway to obtain structurally different *N*-triflyl sulfoximines, and, if possible, to keep in mind the sustainability of these reactions. Finally, we wanted to test the stability and reactivity of these compounds with further functionalization reactions. Herein, we report complementary strategies for the synthesis of *N*-triflyl sulfoximines by oxidation of *N*-trifluoromethylthio sulfoximines (Scheme 1c),^{49,50} as well as some further functionalization reactions and stability experiments. For the majority of our products, we used solid sodium hypochlorite pentahydrate ($\text{NaOCl} \cdot 5\text{H}_2\text{O}$),⁵¹ which we also used in our previous work for the oxidation of *N*-trifluoromethylthio sulfoximines to their sulfinyl derivatives.⁵² $\text{NaOCl} \cdot 5\text{H}_2\text{O}$ in water proved to be a mild oxidation system especially for aryl methyl sulfides, while $\text{NaOCl} \cdot 5\text{H}_2\text{O}$ in a mixture of water and MeCN worked better for bulkier aryl-, alkyl-, and diaryl-sulfides. Finally, *m*-CPBA in DCM was used for chloro-, bromo-, and cyano-substituted substrates, as well as for those with benzyl groups which could not be oxidized by the two previous methods.

Results and discussion

$\text{NaOCl} \cdot 5\text{H}_2\text{O}$ in water was the first oxidation system we tested and it gave good results (Table 1, entry 1). Increasing the excess of $\text{NaOCl} \cdot 5\text{H}_2\text{O}$ (3.2 equiv.) to convert the leftover sulfoxide **4a** produced *N*-Cl sulfoximine as well as an unknown side-product, having no effect on the conversion of the reaction

Table 1 Screening of solvents^a

		Relative ratio ^b (%)		
Entry	Solvent	2a	3a	4a
1	H ₂ O	—	85	15
2	H ₂ O	— ^c	85	—
3	EtOH	75 ^d	—	—
4	MeOH	99	Trace	Trace
5	MeCN	—	34	66
6	EtOAc	— ^c	31	64
7	DCM	26	—	74
8	Hexane	19	4	77
9	Toluene	— ^c	3	97

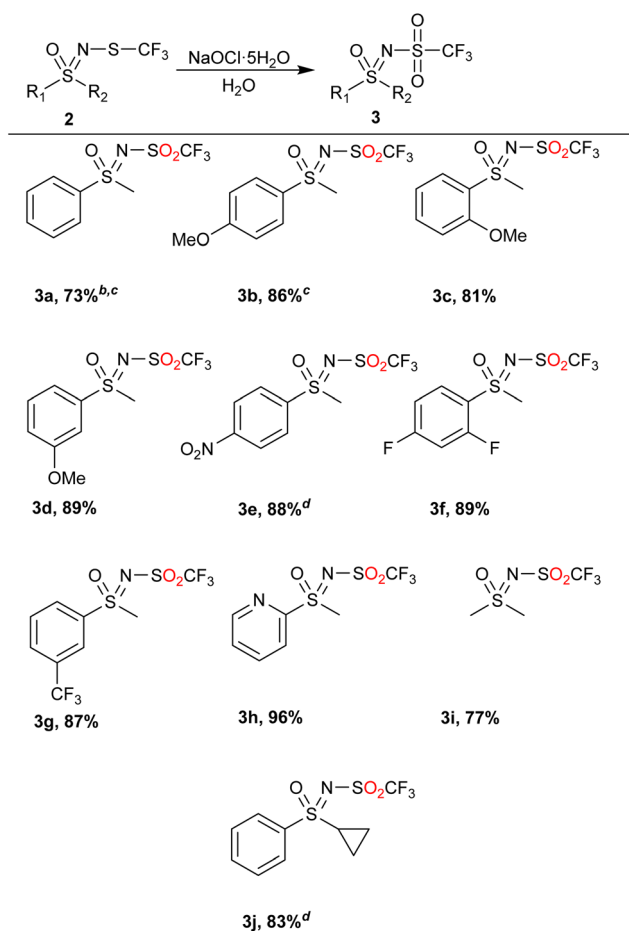
^a Reaction conditions: **2a** (0.1 mmol), solvent 0.3 mL, $\text{NaOCl} \cdot 5\text{H}_2\text{O}$ (2.2 equiv.), stirring 16 h. ^b Determined by ¹H and ¹⁹F NMR. ^c Observed the formation of *N*-chloro sulfoximine. ^d 25% of SONH present.

(Table 1, entry 2). Other solvents were also tested. The reaction does not occur in ethanol (Table 1, entry 3), instead 25% of the *N*-trifluoromethylthio sulfoximine **2a** was converted to the parent NH-sulfoximine. In methanol (Table 1, entry 4) only traces of products **3a** and **4a** are visible, otherwise no changes to the substrate are observed. We assume that the alcohols are oxidized to their corresponding aldehyde or carboxylic acid instead. MeCN and EtOAc (Table 1, entries 5 and 6) behaved similarly, with the majority of the product being in the form of the sulfoxide **4a**. Some *N*-Cl was also present in EtOAc. DCM, hexane and toluene (Table 1, entries 7, 8 and 9) were all more selective for the sulfoxide **4a**, with minimal sulfone **3a** being present in the reaction mixture, indicating that more non-polar solvents promote single oxidation to sulfoxide.

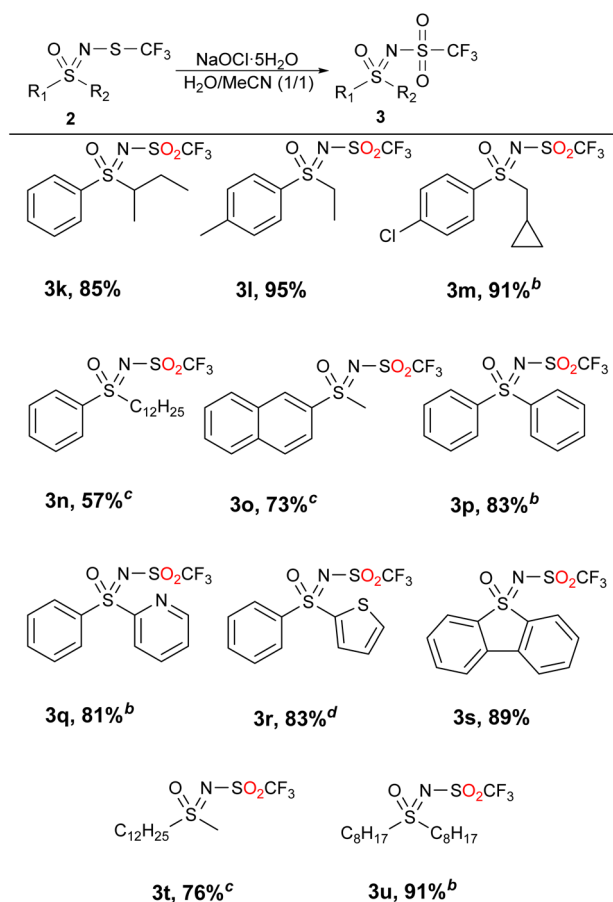
$\text{NaOCl} \cdot 5\text{H}_2\text{O}$ in water was then chosen as a suitable starting point with a simple water/EtOAc workup extraction to isolate the products (Table 2). If the crude product contained some sulfoxide **4** (less than 20%), the product was purified by flash chromatography. If more sulfoxide **4** was present, the reaction was repeated with more oxidant. If other, less polar impurities were present besides the starting substrate **2** or sulfoxide **4**, the product was further purified by column chromatography.

Phenyl methyl sulfide **2a** and monosubstituted phenyl rings bearing the methoxy **2b–2d** or nitro **2e** group as well as the fluoro-disubstituted **2f** underwent the reaction in good to excellent yields, with only the products **3a** and **3b** requiring flash chromatography. Using this method, we also succeeded in obtaining the products **3g** and **3h**, a trifluoromethyl and heterocyclic product, respectively. Smaller alkyl sulfoximines could also be reacted and furnished the product **3i** in 77% yield. Lastly, the substrate **2j**, bearing a cyclopropyl group, was investigated. Although more $\text{NaOCl} \cdot 5\text{H}_2\text{O}$ had to be used, the product was still obtained in good yield. In general, the method



Table 2 Substrate scope^a

^a Reaction conditions: **2** (0.3 mmol), H₂O (1 mL), NaOCl·5H₂O (2.5 equiv.), stirring 16 h. ^b 2.2 equiv. of NaOCl·5H₂O was used. ^c Flash chromatography was used to purify the product. ^d Additional NaOCl·5H₂O was added to the reaction mixture after 16 h (1 equiv.).

Table 3 Substrate scope^a

^a Reaction conditions: **2** (0.3 mmol), H₂O (0.5 mL), MeCN (0.5 mL), NaOCl·5H₂O (2.5 equiv.), stirring 16 h. ^b Flash chromatography was used to purify the product. ^c Column chromatography was used to purify the product. ^d Additional NaOCl·5H₂O was added to the reaction mixture after 16 h (2 equiv.).

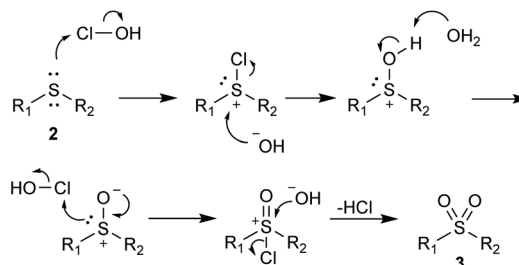
exhibited several important green attributes (water as a reaction medium, high selectivity, room temperature and low amount of non-hazardous waste).

The bulkier substrates posed a challenge under the reaction conditions used in Table 2 with sulfoxide **4** as the most isolated product or a 1 : 1 mixture of sulfone **3** and sulfoxide **4**. Adding more NaOCl·5H₂O did not move the reaction towards sulfones, so an alternative was sought. By adding MeCN to water, more favorable results were obtained and previously difficult to access sulfones were isolated with very good yields and mostly no need for purification (Table 3). We suspect that the increased solubility of the substrates was the decisive factor.

The products with longer and branched alkyl chains **3k**, **3l**, **3m** and **3u** were isolated in good to excellent yields, while the substrates with the dodecyl group (**2n** and **2t**) also produced products **3n** and **3t** in 57% and 76% yield, respectively. The diaryl substrates **2p–2s** reacted smoothly, although they produced some traces of sulfoxides, which were easily removed by flash chromatography. The product **3o**, containing the bulkier naphthyl group, was also successfully obtained.

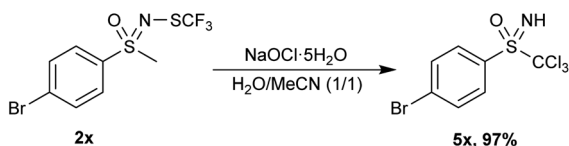
Although acetonitrile was present in the reaction medium, the transformation is in good accordance with green chemistry principles. A mechanism is probably similar to the previously proposed⁵¹ and is comprised of a chlorination of the sulfur atom and subsequent attack by the hydroxide ion (Scheme 2).

However, the method used in Table 3 was not suitable for 4-chloro **2w**, 4-bromo **2x** and 4-cyano **2y** aryl methyl substrates. **2w**



Scheme 2 Proposed mechanism for the oxidation of sulfides **2** to their corresponding sulfones **3** with NaOCl·5H₂O.





Scheme 3 Removal of trifluoromethylthio group with concomitant chlorination.

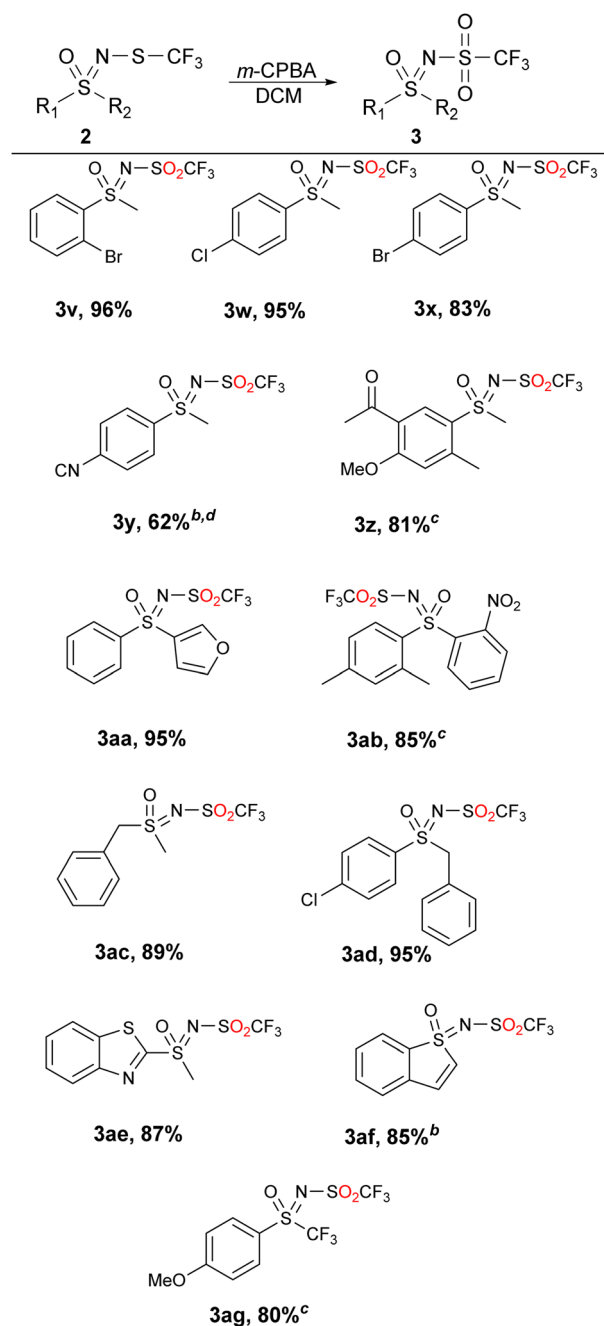
could not exceed 60% conversion even when additional NaOCl·5H₂O was introduced. **2y** produced various chloroform-insoluble compounds, while **2x** underwent deprotection of the *N*-trifluoromethylthio group to NH-sulfoximine. In addition, the methyl group adjacent to the sulfoximine was chlorinated, replacing all the hydrogen atoms (Scheme 3, **5x**). The product **5x** decomposed rapidly and could not be purified by chromatographical means. The reactivity of 4-bromo derivative **2x** is somewhat anomalous, since 4-chloro and 4-methoxy analogues **2w** and **2b** reacted smoothly, giving **3w** and **3b** in high yields.

These, and the other substrates that could not be quantitatively oxidized to sulfones by the two previous methods were successfully transformed to *N*-triflyl sulfoximines **3** using *m*-CPBA in DCM (Table 4). The latter method can be used with all substrates contained herein, but generates the highest amount of waste (the benzoic acid leftover as well as the Na₂CO₃ that is needed in the extraction step). With sustainability and waste minimization in mind, we opted to present all three methods instead of using only *m*-CPBA for all substrates.

Substrates with halogen-substituted phenyl groups **2v–2x** were readily oxidized to the corresponding sulfones **3v–3x**. The substrate with the benzonitrile group **2y** proved to be challenging and required more oxidant and flash chromatography. **2z**, which contains the methyl ketone group, formed a number of impurities in very small amounts and had to be purified by column chromatography. The sterically hindered **2ab** produced some minor impurities that required column chromatography, while the functionalization of benzylic substrates **2ac** and **2ad** proceeded without any major difficulties. Transformation of the heterocyclic substrates **2ae** and **2af** also proceeded smoothly and with good yields. The product **3ag** was also obtained in 80% yield despite the inclusion of the trifluoromethyl group. Mechanistically we hypothesize that the reaction occurs with the nucleophilic attack of the sulfide towards the peroxide, similar as it does with hydrogen peroxide⁴⁵ and furnishing the *m*-chlorobenzoic acid (Scheme 4).

For further clarification, a table with all substrates and their corresponding oxidation system is provided (Table 5). NaOCl·5H₂O in water is suitable for most phenyl methyl substrates and smaller dialkyl substrates. Interestingly, substrates with chloro- and bromo-substituted phenyl rings **2v–2x** appear to be outliers from this theory, although both 4-MeO **2b** and 4-NO₂ **2e** were successfully converted to their corresponding sulfones **3b** and **3e**. Reasons might be complex, since they could not be attributed to the stereoelectronic effects and solubility issues. As mentioned above, the addition of MeCN assisted the oxidation of some sterically hindered and more hydrophobic substrates, which most likely suffered from

Table 4 Substrate scope^a



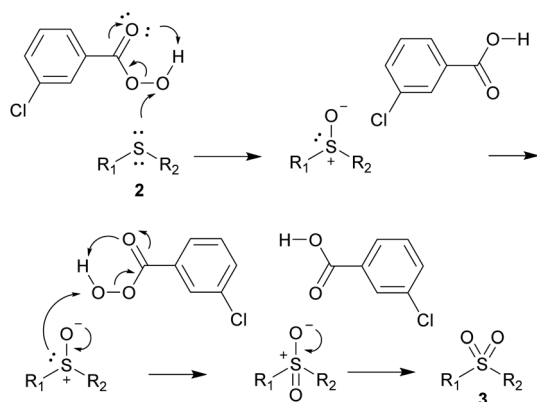
^a Reaction conditions: **2** (0.3 mmol), DCM (1 mL), *m*-CPBA (2.5 equiv.), stirring 16 h. ^b Flash chromatography was used to purify the product.

^c Column chromatography was used to purify the product.

^d Additional *m*-CPBA was added to the reaction mixture after 16 h (1 equiv.).

decreased solubility. Products that could not be obtained with these two methods (Tables 2 and 3) were obtained with *m*-CPBA in DCM (Table 4). It can be concluded that the effect of structure of starting **2** on oxidation is multifaceted, and it is rather challenging to match the method with the structure of the starting material **2**.





Scheme 4 Proposed mechanism for the oxidation of sulfides **2** with *m*-CPBA.

Each method was also tested at the gram-scale, with encouragingly higher yields of **3a**, **3p** and **3x** were obtained compared to the 0.3 mmol scale (Scheme 5).

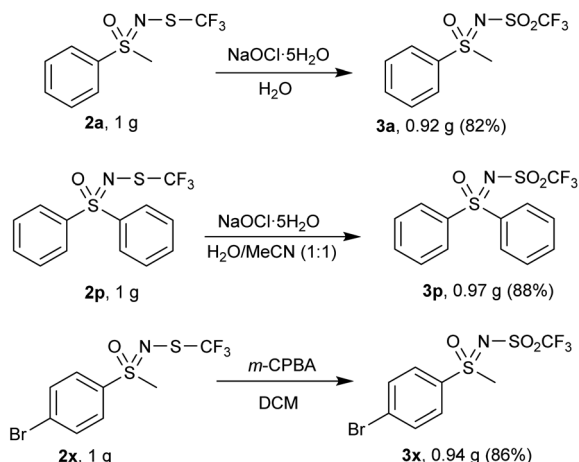
Although compounds **3** have been synthesized previously, to the best of our knowledge there are few examples of reactions in which they assume the role of reactants.⁵³ We therefore decided to test the stability of *N*-triflyl sulfoximines **3** under different conditions. **3a** was exposed to aqueous solutions of 37% HCl and 50% NaOH, both of which showed no effect even after prolonged exposure at room temperature (24 h). Elevated temperature (120 °C) also had no effect other than melting the compound.

Using standard Suzuki–Miyaura conditions, the coupling of **3x** and 4-methylbenzeneboronic acid was achieved and the product **3ah** was isolated in 88% yield (Scheme 6a). Similarly, **3x** was successfully coupled with phenylacetylene in Et₃N with

Table 5 Overview of all the substrates and their corresponding oxidation systems

Substrate	R ₁	R ₂	Oxidation system	Yield	Substrate	R ₁	R ₂	Oxidation system	Yield
2a	Ph	Me	NaOCl·5H ₂ O, H ₂ O	73%	2r	Ph	2-Thiophenyl	NaOCl·5H ₂ O, H ₂ O/MeCN	83%
2b	4-MeO-C ₆ H ₄	Me	NaOCl·5H ₂ O, H ₂ O	86%	2s	Dibenzo[<i>b,d</i>]thiophenyl		NaOCl·5H ₂ O, H ₂ O/MeCN	89%
2c	2-MeO-C ₆ H ₄	Me	NaOCl·5H ₂ O, H ₂ O	81%	2t	Dodecyl	Me	NaOCl·5H ₂ O, H ₂ O/MeCN	76%
2d	3-MeO-C ₆ H ₄	Me	NaOCl·5H ₂ O, H ₂ O	89%	2u	Octyl	Octyl	NaOCl·5H ₂ O, H ₂ O/MeCN	91%
2e	4-NO ₂ -C ₆ H ₄	Me	NaOCl·5H ₂ O, H ₂ O	88%	2v	2-Br-C ₆ H ₄	Me	<i>m</i> -CPBA, DCM	96%
2f	2,4-F-C ₆ H ₃	Me	NaOCl·5H ₂ O, H ₂ O	89%	2w	4-Cl-C ₆ H ₄	Me	<i>m</i> -CPBA, DCM	95%
2g	3-CF ₃ -C ₆ H ₄	Me	NaOCl·5H ₂ O, H ₂ O	87%	2x	4-Br-C ₆ H ₄	Me	<i>m</i> -CPBA, DCM	83%
2h	2-Pyridyl	Me	NaOCl·5H ₂ O, H ₂ O	96%	2y	4-CN-C ₆ H ₄	Me	<i>m</i> -CPBA, DCM	62%
2i	Me	Me	NaOCl·5H ₂ O, H ₂ O	77%	2z		Me	<i>m</i> -CPBA, DCM	81%
2j	Ph	Cyclopropyl	NaOCl·5H ₂ O, H ₂ O	83%					
2k	Ph	<i>sec</i> -Butyl	NaOCl·5H ₂ O, H ₂ O/MeCN	85%	2aa	Ph	3-Furanyl	<i>m</i> -CPBA, DCM	95%
2l	4-Tolyl	Et	NaOCl·5H ₂ O, H ₂ O/MeCN	95%	2ab	2,4-Me-C ₆ H ₃	2-NO ₂ -C ₆ H ₄	<i>m</i> -CPBA, DCM	85%
2m	4-Cl-C ₆ H ₄	Cyclopropylmethyl	NaOCl·5H ₂ O, H ₂ O/MeCN	91%	2ac	Benzyl	Me	<i>m</i> -CPBA, DCM	89%
2n	Ph	Dodecyl	NaOCl·5H ₂ O, H ₂ O/MeCN	57%	2ad	Benzyl	4-Cl-C ₆ H ₄	<i>m</i> -CPBA, DCM	95%
2o	Naphthyl	Me	NaOCl·5H ₂ O, H ₂ O/MeCN	73%	2ae	Benzo[<i>d</i>]thiazolyl	Me	<i>m</i> -CPBA, DCM	87%
2p	Ph	Ph	NaOCl·5H ₂ O, H ₂ O/MeCN	83%	2af	Benzo[<i>d</i>]thiophenyl		<i>m</i> -CPBA, DCM	85%
2q	Ph	2-Pyridyl	NaOCl·5H ₂ O, H ₂ O/MeCN	81%	2ag	4-MeO-C ₆ H ₄	CF ₃	<i>m</i> -CPBA, DCM	80%

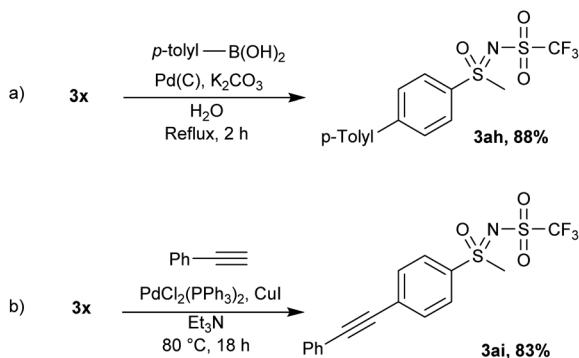
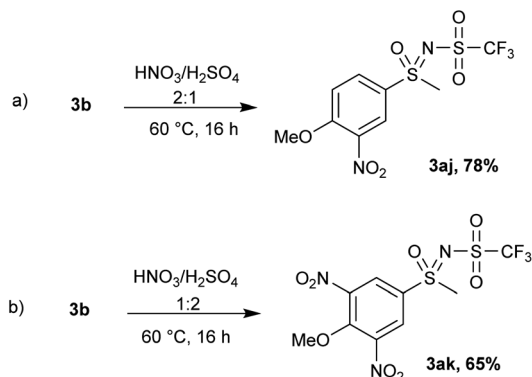
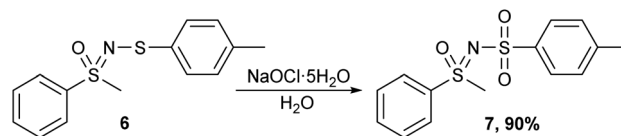




Scheme 5 Gram scale reactions.

catalytic amounts of palladium and copper furnishing **3ai** in 83% yield (Scheme 6b).

An *N*-triflyl sulfoximine with an electron-donating group (4-methoxy) **3b** was used in an electrophilic aromatic substitution reaction (Scheme 7). By heating **3b** in nitric acid (63% solution) overnight, 25% conversion was observed and no further changes in the substrate were detected. Addition of sulfuric acid (ratio of HNO₃ : H₂SO₄ = 2 : 1) led to the mononitrated product

Scheme 6 Further functionalizations of **3x**.Scheme 7 Nitration of **3b**.Scheme 8 Oxidation of *N*-sulfonylated sulfoximine.

3aj with complete conversion (Scheme 7a), while switching the ratio of acids and using more H₂SO₄ promoted the formation of a dinitrated product **3ak** (Scheme 7b). We reason that the addition of more H₂SO₄ increases the concentration of the nitronium ion (NO₂⁺), which promotes further nitration. When fuming nitric acid (90% solution) was used, a mixture of both nitration products (**3aj** and **3ak**) was formed.

Other reaction conditions were also investigated, which provided further insight into the stability and reactivity of compounds **3**. Attempts to reduce the triflyl group to a sulfoxide or sulfide were unsuccessful. The reducing agents used included NaSH·H₂O in HCl, NaBH₄ in EtOH and LiAlH₄ in THF; all of which are used in literature for various reductions of sulfones and sulfoxides. Substrate **3a** remained unchanged, only the latter reducing agent led to some decomposition. The product **3x** remained unchanged when a Grignard reaction with *i*-PrMgCl was attempted. Bromination with bromine in acetic acid, the classic Friedel–Crafts reaction with acetyl chloride and AlCl₃ in DCM and a variation of this reaction in TFA with acetic anhydride had no effect on substrate **3b**. Reactions of **3a** with *n*-butyllithium led to decomposition of the substrate into many unknown compounds. From this, we can infer that compounds **3** have good resistance under a wide range of conditions, implying that the functional group would remain intact in further functionalization reactions of larger compounds.

Finally, the methods were tested on a non-*N*-trifluoromethylthio sulfoximine compound. For this purpose, an *N*-sulfonylated sulfoximine **6** was prepared and oxidized using all three methods. All three methods successfully afforded the corresponding sulfone **7** (Scheme 8), with *m*-CPBA being the least desirable oxidizing agent as it also produced some minor impurities that would require purification.

Conclusion

In conclusion, new oxidative methods for obtaining *N*-triflyl sulfoximines as well as *N*-sulfonyl sulfoximines were reported. By using NaOCl·5H₂O in water, this relatively green approach is able to oxidize most phenyl methyl sulfoximines in good yields with little need for additional purification. This method was also used for the oxidation of *N*-sulfonyl sulfoximines. A mixture of water and MeCN was required for bulky substrates, while *m*-CPBA in DCM was needed for benzyl, heavily-substituted aryl systems, and bromo-, chloro-, and cyano-substituted rings. The stability of *N*-triflyl sulfoximines was studied and no degradation was observed in concentrated aqueous NaOH and HCl solutions or at elevated temperatures. Furthermore, mono- and dinitration occurred in concentrated nitric and sulfuric acid.



The *N*-triflyl group also proved to be tolerant to the Suzuki–Miyaura and Sonogashira coupling reaction conditions and gave both products in good yields.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

Ž. T.: investigation, validation, data curation, writing – original draft and writing – review & editing. M. J.: conceptualization, resources, validation, supervision, writing – original draft and writing – review & editing.

Conflicts of interest

There are no conflicts of interest to declare.

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References

- U. Lücking, *Org. Chem. Front.*, 2019, **6**, 1319–1324.
- M. Frings, C. Bolm, A. Blum and C. Gnamm, *Eur. J. Med. Chem.*, 2017, **126**, 225–245.
- Y. Han, K. Xing, J. Zhang, T. Tong, Y. Shi, H. Cao, H. Yu, Y. Zhang, D. Liu and L. Zhao, *Eur. J. Med. Chem.*, 2021, **209**, 112885.
- P. Mäder and L. Kattner, *J. Med. Chem.*, 2020, **63**, 14243–14275.
- U. Lücking, *Chem.–Eur. J.*, 2022, **28**, e202201993.
- M. L. G. Borst, C. M. J. Ouairy, S. C. Fokkema, A. Cecchi, J. M. C. A. Kerckhoffs, V. L. De Boer, P. J. Van Den Boogaard, R. F. Bus, R. Ebens, R. Van Der Hulst, J. Knol, R. Libbers, Z. M. Lion, B. W. Settels, E. De Wever, K. A. Attia, P. J. Sinnema, J. M. De Gooijer, K. Harkema, M. Hazewinkel, S. Snijder and K. Pouwer, *ACS Comb. Sci.*, 2018, **20**, 335–343.
- P. Devendar and G. F. Yang, *Top. Curr. Chem.*, 2017, **375**, 1–44.
- C. Gnamm, A. Jeanguenat, A. C. Dutton, C. Grimm, D. P. Kloer and A. J. Crossthwaite, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 3800–3806.
- Y. Xie, H. Li, D. Liu, L. Zhao, X. Liu, X. Liu and Y. Li, *J. Agric. Food Chem.*, 2024, **72**, 11716–11723.
- H. Okamura and C. Bolm, *Chem. Lett.*, 2004, **33**, 482–487.
- S. Sau, K. Mukherjee, K. Kondalarao, V. Gandon and A. K. Sahoo, *Org. Lett.*, 2023, **25**, 7667–7672.
- P. Ghosh, B. Ganguly and S. Das, *Asian J. Org. Chem.*, 2020, **9**, 2035–2082.
- R. Luisi and J. A. Bull, *Molecules*, 2023, **28**, 1120.
- M. T. Zambri, C. Ho and M. S. Taylor, *Org. Lett.*, 2023, **25**, 8274–8278.
- M. Kumar, A. Rastogi, Raziullah, A. Ahmad, M. K. Gangwar and D. Koley, *Org. Lett.*, 2022, **24**, 8729–8734.
- C. J. Dodd, D. C. Schultz, J. Li, C. W. Lindsley and A. M. Bender, *Org. Biomol. Chem.*, 2023, **21**, 5181–5184.
- P. Shi, Y. Tu, D. Ma and C. Bolm, *Adv. Synth. Catal.*, 2023, **365**, 1613–1617.
- N. S. George, M. Kosiuha, A. Moquette and C. Parsy, *Eur. J. Org. Chem.*, 2022, **2022**, e202201219.
- P. Xu, W. Su and T. Ritter, *Chem. Sci.*, 2022, **13**, 13611–13616.
- N. Chakraborty, K. K. Rajbongshi, A. Dahiya, B. Das, A. Vaishnani and B. K. Patel, *Chem. Commun.*, 2023, **59**, 2779–2782.
- W. Su, P. Xu, R. Petzold, J. Yan and T. Ritter, *Org. Lett.*, 2023, **25**, 1025–1029.
- N. Chakraborty, K. K. Rajbongshi, A. Gondaliya and B. K. Patel, *Org. Biomol. Chem.*, 2024, **22**, 2375–2379.
- X. Kang, H. Wang and Q. Zeng, *Eur. J. Org. Chem.*, 2022, **2022**, e202201229.
- L. Yang, J. Feng, M. Qiao and Q. Zeng, *Org. Chem. Front.*, 2017, **5**, 24–28.
- D. Kong, D. Ma, P. Wu and C. Bolm, *ACS Sustain. Chem. Eng.*, 2022, **10**, 2863–2867.
- S. Zhang, M. Hu, C. Qin, S. Wang, F. Ji and G. Jiang, *New J. Chem.*, 2024, **48**, 2576–2583.
- X. Li, J. Huang, L. Xu, J. Liu and Y. Wei, *Adv. Synth. Catal.*, 2023, **365**, 4647–4653.
- W. Zhang, D. Jin, Y. Hu, K. Yin, Q. Zou, L. Tang and P. Qian, *J. Org. Chem.*, 2024, **89**, 6106–6116.
- D. Kong, M. M. Amer and C. Bolm, *Green Chem.*, 2022, **24**, 3125–3129.
- P. Shi, Y. Tu, D. Zhang, C. Wang, K. N. Truong, K. Rissanen and C. Bolm, *Adv. Synth. Catal.*, 2021, **363**, 2552–2556.
- H. S. Veale, J. Levin and D. Swern, *Tetrahedron Lett.*, 1978, **19**, 503–506.
- D. M. Ketcha and D. Swern, *Synth. Commun.*, 1984, **14**, 915–919.
- S. L. Huang and D. Swern, *J. Org. Chem.*, 1979, **44**, 2510–2513.
- K. Akutagawa, N. Furukawa and S. Oae, *J. Org. Chem.*, 1984, **49**, 2282–2284.
- M. Klein, D. L. Troglauer and S. R. Waldvogel, *JACS Au*, 2023, **3**, 575–583.
- H. Kwart and A. A. Kahn, *J. Am. Chem. Soc.*, 1967, **89**, 1950–1951.
- Y. C. Gae and C. Bolm, *Org. Lett.*, 2005, **7**, 4983–4985.
- Y. Liu, H. Wang and X. Yang, *Tetrahedron*, 2019, **75**, 4697–4702.
- J. F. K. Müller and P. Vogt, *Tetrahedron Lett.*, 1998, **39**, 4805–4806.
- H. Okamura and C. Bolm, *Org. Lett.*, 2004, **6**, 1305–1307.
- O. G. Mancheño and C. Bolm, *Org. Lett.*, 2006, **8**, 2349–2352.



- 42 G. Y. Cho and C. Bolm, *Tetrahedron Lett.*, 2005, **46**, 8007–8008.
- 43 A. Yoshimura, V. N. Nemykin and V. V. Zhdankin, *Chem.–Eur. J.*, 2011, **17**, 10538–10541.
- 44 W. Zheng, M. Tan, L. Yang, L. Zhou and Q. Zeng, *Eur. J. Org. Chem.*, 2020, **2020**, 1764–1768.
- 45 H. Nie, Z. Xiong, M. Hu, S. Zhang, C. Qin, S. Wang, F. Ji and G. Jiang, *J. Org. Chem.*, 2023, **88**, 2322–2333.
- 46 M. Ochiai, M. Naito, K. Miyamoto, S. Hayashi and W. Nakanishi, *Chem.–Eur. J.*, 2010, **16**, 8713–8718.
- 47 D. Craig, N. J. Geach, C. J. Pearson, A. M. Z. Slawin, A. J. P. White and D. J. Williams, *Tetrahedron*, 1995, **51**, 6071–6098.
- 48 N. Thota, P. Makam, K. K. Rajbongshi, S. Nagiah, N. S. Abdul, A. A. Chuturgoon, A. Kaushik, G. Lamichhane, A. M. Somboro, H. G. Kruger, T. Govender, T. Naicker and P. I. Arvidsson, *ACS Med. Chem. Lett.*, 2019, **10**, 1457–1461.
- 49 C. Bohnen and C. Bolm, *Org. Lett.*, 2015, **17**, 3011–3013.
- 50 A. Zupanc and M. Jereb, *J. Org. Chem.*, 2021, **86**, 5991–6000.
- 51 M. Kirihara, T. Okada, Y. Sugiyama, M. Akiyoshi, T. Matsunaga and Y. Kimura, *Org. Process Res. Dev.*, 2017, **21**, 1925–1937.
- 52 Ž. Testen and M. Jereb, *Org. Biomol. Chem.*, 2024, **22**, 2012–2020.
- 53 D. Craig, F. Grellepois and A. J. P. White, *J. Org. Chem.*, 2005, **70**, 6827–6832.

