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Synthesis of NH-Sulfoximines Using Recyclable Hypervalent Iodine (III) Reagents under Aqueous Micellar Conditions

Guocai Zhang,[#[a][b]] Hongsheng Tan,[#[a]] Weichun Chen,[[b]] Hong C. Shen,[[b]] Yue Lu,[[a]] Changwu Zheng*[[a]] and Hongxi Xu*[[c]]

Abstract: The synthesis of NH-sulfoximines from sulfides has been first developed under a mild, sustainable condition in an aqueous solution with surfactant TPGS-750-M as the catalyst at room temperature. In this newly developed process, a simple and convenient recyclable strategy to regenerate the indispensable hypervalent iodine(III) was utilized. The resulting 1,2,3-trifluoro-5-iodobezene could be recovered almost quantitively from the mixture by liquid-liquid extraction, and then oxidized to the corresponding iodine (III) species. This optimized protocol is compatible with a broad range of functional groups and could be easily performed on a gram scale. Thus, this novel method provides a new and green protocol for the synthesis of sulfoximines.

Sulfoximine-containing compounds have been studied extensively over the past decades for their biological activities and potential medicinal utilities.[1] The interesting dual functionality of sulfoximine as both a hydrogen donor and acceptor increase its utility in drug discovery.[2] Several sulfoximine-containing compounds have been reported as drug candidates (Figure 1). For example, the analogue of the COX-2 inhibitor Rofecoxib showed a good COX-2 selectivity and a lower hERG activity, and the pan-CDK inhibitor BAY 100394 is used to treat solid tumor with an abnormality in Mcl-1, Myc or CCNE, which is currently in phase II clinical trials.[3]

Due to the importance of sulfoximines in medicinal chemistry, tremendous efforts have been dedicated to the development of practical synthetic methods to access sulfoximines.[4] Typical method involves the use of sulfoxides as starting materials and transition metals (Fe, Rh, Cu) as the catalysts, by which the *N*-protected sulfoximines can be prepared via electrophilic transfer of an NR group from sulfonamide, trifluoroacetamide, carbamate or amide.[5,6] In order to obtain the free NH-sulfoximines, an additional de-protection step is herein needed.[7] To improve the synthetic efficacy, direct synthesis of NH-sulfoximines from sulfoxides was then developed by several groups[8] using hydroxylamines (or salts) as the NH source under metal catalysis or using ammonium carbamate with diacetoxyiodobenzene as the oxidant. The free nitrogen group on NH-sulfoximines increases the molecular diversity and provides the possibility for further functionalization. Recently, a more efficient and direct synthesis of NH-sulfoximines has been achieved from sulfides under metal-free conditions by Bull, Luisi, and two other research groups separately (Scheme 1a).[9] Using excess diacetoxyiodobenzene as the oxidant, a highly chemo-selective *N* and *O* group transfer to sulfides was achieved in MeOH.

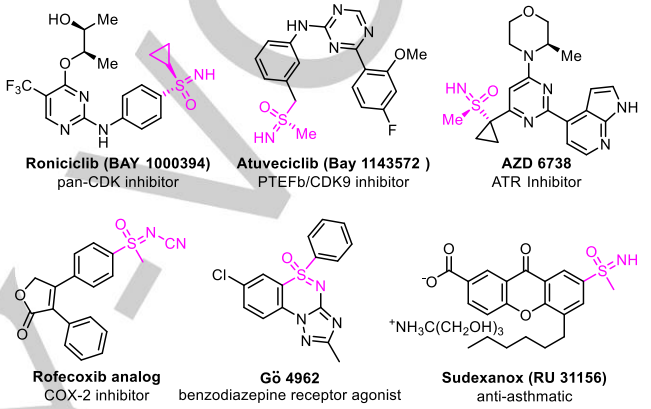
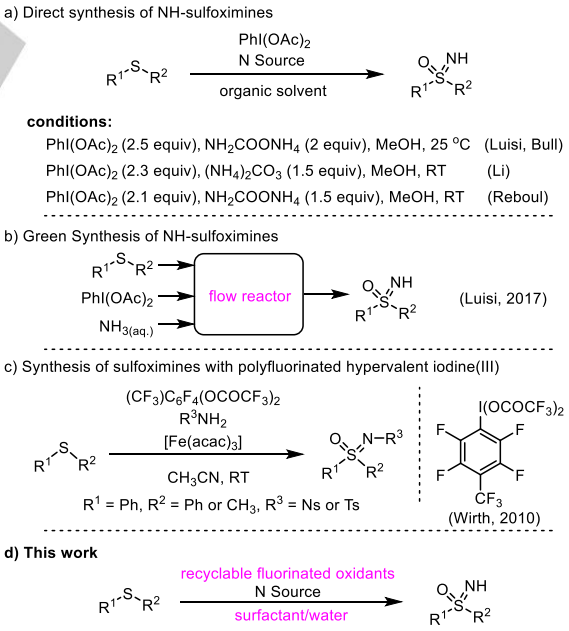


Figure 1. Representative sulfoximine-containing compounds with important biological activities.



Scheme 1. Direct synthesis of NH-sulfoximines from sulfides and the sustainable strategy.

Following these pioneer work, Luisi group then developed a convenient, mild, and green synthesis of NH-sulfoximines in flow reactors in view of efficient and safe synthesis for industrial

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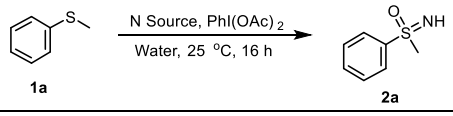
applications[10] (Scheme 1b). Similar continuous flow strategy was also used in the synthesis of *N*-protected sulfoximines[11] and pharmaceutically relevant morpholino-pyrimidines with a sulfoximine moiety[12] by Lebel and Kappe group, respectively. Notwithstanding the enormous progress made for preparing the sulfoximines, and with respect to large-scale manufacturing, sustainability and environmentally friendly process development, it would be greatly ideal to perform the reactions in water[13] and recycle the excess oxidants. However, commonly used hypervalent iodine(III) compounds such as $PhI(OAc)_2$ and $PhI(OCOCF_3)_2$ have low solubility in water and it is difficult to recycle. To improve the solubility, Kita's group has developed a micellar system using quaternary ammonium salt as the surfactant on the oxidation of sulfides to sulfoxides with iodosobenzene in water.[14] Recently, a versatile and highly reactive polyfluorinated hypervalent iodine(III) compound was reported by Wirth group and the application to synthesize sulfoximines from sulfides was also demonstrated (Scheme 1c).[15] Because polyfluorinated hypervalent iodine(III) compounds show increased reactivity and solubility and are easy to recycle,[16] therefore, a combination of the polyfluorinated hypervalent iodine reagents and surfactants in water would be an ideal solution for the environmentally benign synthesis of sulfoximines.

Table 1. Optimization of reaction conditions[a]

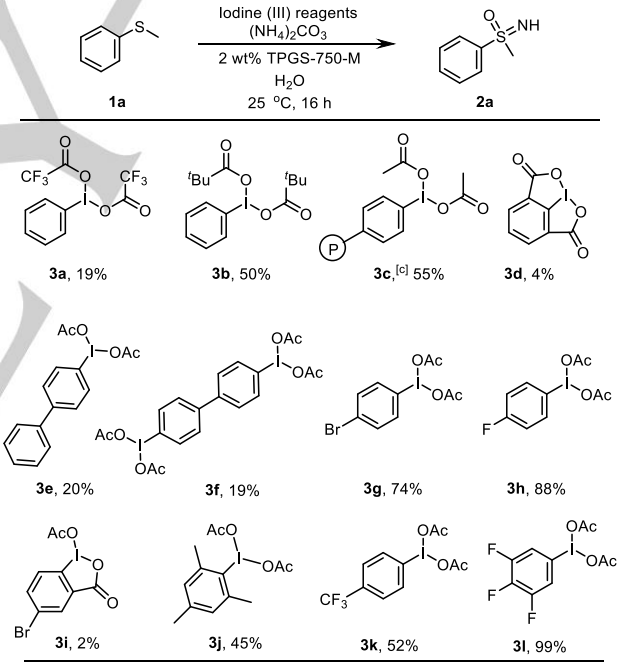


Entry	Solvent	N sources (equiv.)	Yield[b]
1	Neat water	$NH_2CO_2NH_4$ (2.0)	64%
2	2 wt% PEG 400	$NH_2CO_2NH_4$ (2.0)	77%
3	2 wt% Tween 80	$NH_2CO_2NH_4$ (2.0)	55%
4	1 wt% TPGS-750-M	$NH_2CO_2NH_4$ (2.0)	76%
5	2 wt% TPGS-750-M	$NH_2CO_2NH_4$ (2.0)	85%
6	3 wt% TPGS-750-M	$NH_2CO_2NH_4$ (2.0)	79%
7	5 wt% TPGS-750-M	$NH_2CO_2NH_4$ (2.0)	82%
8	2 wt% Nok	$NH_2CO_2NH_4$ (2.0)	81%
9	2 wt% TPGS-750-M	NH_2OAc (2.0)	83%
10	2 wt% TPGS-750-M	$NH_3{\cdot}H_2O$ (2.0)	55%
11	2 wt% TPGS-750-M	NH_4Cl (2.0)	0%
12	2 wt% TPGS-750-M	NH_4Br (2.0)	0%
13	2 wt% TPGS-750-M	NH_4I (2.0)	0%
14	2 wt% TPGS-750-M	$(NH_4)_2CO_3$ (2.0)	91%

[a] Reaction conditions: **1a** (0.25 mmol), $PhI(OAc)_2$ (0.75 mmol), ammonium source (1.0 mmol), water (1 mL), room temperature, 16 h. [b] Isolated yield.

At the outset, we began our investigation by using thioanisole as the model substrate, $PhI(OAc)_2$ as the initial oxidant and $NH_2CO_2NH_4$ as the nitrogen source in water at room temperature. Without the surfactant, the desired sulfoximine was obtained in only 64% yield probably due to the poor solubility of thioanisole and $PhI(OAc)_2$ in water (Table 1, entry 1). Since 2008, the Lipshutz group has published a series of papers, aiming to mimic nature's processes that produce chemicals by employing water as the reaction medium. For this purpose, several generations of surfactants have been designed and applied, including TPGS-750-M and Nok (SPGS-550-M) under micellar catalysis to overcome the challenges of running reactions in water.[17] Therefore, several surfactants including the TPGS-750-M were added to water separately to improve the solubility of the lipophilic reagents. To our delight, the addition of 2 wt% PEG-400 in reaction afforded the product in 77% yield (Table 1, entry 2). However, only 55% yield of sulfoximine (**2a**) was obtained with 2 wt% tween 80, likely due to a lot of white solid precipitation (Table 1, entry 3). Interestingly, TPGS-750-M as a promoter in water showed great compatibility, leading to a 76% yield of the desired product. Further screening of the weight ratio of TPGS-750-M from 2% wt to 5% wt concluded that the reaction was most efficient when it was performed at 2 wt% (Table 1, entries 4-7). In addition, 2% Nok, which is the third generation of amphiphilic surfactant, also provided an excellent yield (Table 1, entry 8). A screening of other ammonium source (Table 1, entries 9-14) revealed that the yield of **2a** could be improved to 91% by utilizing ammonium carbonate probably due to its good solubility in water and rapid reaction with AcOH from iodine (III) reagents to provide NH_3 smoothly in the aqueous medium (Table 1, entry 14).

Table 2. Screening of hypervalent iodine (III) reagent[a],[b]



[a] Reaction conditions: **1a** (0.25 mmol), **3** (0.75 mmol), ammonium carbonate (1.0 mmol), water (1 mL), room temperature, 16 h. [b] isolated yield. [c] Ⓟ is poly styrene.

In order to develop a more sustainable synthetic method, various hypervalent iodine (III) reagents were investigated so as to develop a recyclable oxidation reagent to decrease the amount of major by-product iodobenzene. As anticipated, the hypervalent iodine (III) reagents play a pivotal role in the outcome of the process, since the reactivity of iodine (III) reagent highly depends on its ligands (Table 2).[18] Only a 19% yield of the expected product was produced in the presence of $PhI(OTFA)_2$ (**3a**), while $PhI(OPiv)_2$ (**3b**) just gave 50% yield. Poly(diacetoxyiodo)styrene **3c**[19], **3d**[20], **3e** and **3f**,[21] known for their good properties to facilitate the separation of the iodoarene co-products from the reaction mixture and the reuse of reagents, did not afford a good

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conversion. The reaction efficiency was obviously affected by the electronic nature of the substituents, as electron-withdrawing groups on the benzene ring generally resulted in a higher conversion in comparison with those containing an electron-donating group (**3g-3h, 3j-3l**). Only a trace amount of target compound was detected when Iodosolactone **3i** were employed. Notably, the highest conversion of **2a** was achieved with the newly prepared diacetoxytrifluoro iodobenzene (**3l**) probably because the fluorine groups on the aromatic moiety enhance the rate initially to form the active intermediate via its electrophilicity and add considerable lipophilicity to **3l** to increase its location inside the micellar cores. The other advantage with the use of **3l** is that it can be easily regenerated by re-oxidation[22] of trifluoroiodobenzene, which can be recovered from the reaction mixture by liquid-liquid extraction in over 80% yield.[23] Compared to the recycling of fluorinated iodine compounds in the reactions with organic solvents,[16] the recovery and isolation procedure in water are more convenient. After the reaction, concentrated aqueous ammonia (35%) was added to the reaction suspension which turned to be a homogeneous phase after stirring. The ammonia acts as a reductant to consume the excess hypervalent iodine (III) reagent and neutralize the acetic acid generated in the reaction. Furthermore, the sulfoximine products exhibit a certain degree of acidity, herein, the addition of concentrated aqueous ammonia (35%) to the mixture also promotes the dissolution of the products in aqueous phase. The mixture was then extracted with *n*-heptane to separate trifluoroiodobenzene almost in quantitive yield. The desired sulfoximines can be directly obtained by additional extraction with dichloromethane from aqueous layer under basic environment with a good yield and high purity (Figure 2). After extraction, the organic phase was dried and distilled under atmospheric pressure. Over 90% of the organic solvents, CH_2Cl_2 and *n*-heptane, can be recycled and reused.

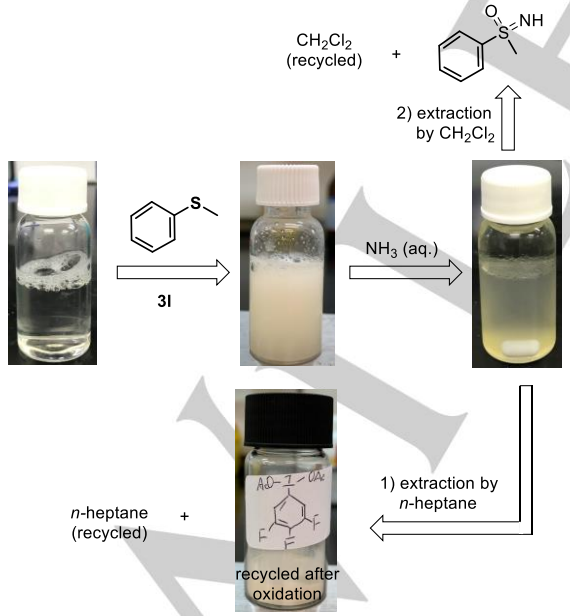
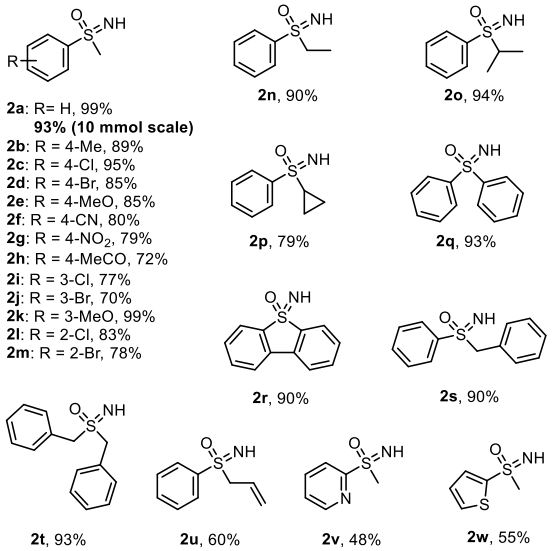


Figure 2. The recovery and isolation process.

Having this optimized reaction condition and recycling method in hand, we explored the scope of substrates **1** for direct synthesis of sulfoximins **2**, and the results are summarized in Scheme 2. In the first reactions, substrates bearing either electron-donating or electron-withdrawing substituents (Me, OMe, Cl, Br, NO_2, CN, MeC=O) at different positions of the aryl moiety could be accommodated to afford the corresponding products (**2a–2m)** in 70%–99% yields. The electronic nature of the aryl moiety and the substituent position on the benzene ring seemed to have little influence on the reaction efficiency. Most of the sulfoximines were obtained in excellent yields. Subsequently, the substrate scope of substituents on both sides of sulfur was then investigated. Generally, the steric effect did not substantially affect the transformation. The substrates bearing phenyl, ethyl, isopropyl, allyl or benzyl group on either side worked well in this reaction (**2n**-**2u**). In addition, heterocycles-containing sulfoximines could be achieved in moderated yields (**2v**-**2w**). However, during the reactions to produce **2u**-**2w**, several undetermined by-products were observed and the yields were decreased, probably due to the over-oxidation of alkene and heteroatoms under these conditions. After the reactions, the trifluoroiodobenzene and sulfoximines were recovered and isolated respectively, according to the standard process in Figure 2. In case of a few sulfoximines with poor solubility in aqueous phase, a small amount of hexafluoroisopropanol (HFIP) can be added as a co-solvent to form a homogeneous phase before the extraction.[24] To evaluate the scalability of the developed method and recyclability of the hypervalent iodine (III) reagent **3l**, the synthesis of **2a** was then conducted in a 10 mmol scale reaction. Gratifyingly, a high yield (93%, 1.4 g) of product was detected after 16 hours with a simple work up process. Upon recycling, trifluoroiodobenzene was recovered from the reaction mixture in 91% yield, and then re-oxidized to **3l** by treating with sodium perborate tetrahydrate and trifluoromethanesulfonic acid in acetic acid solution.[22] The results confirmed the excellent performance of this new protocol that features mild reaction conditions, high efficiency, and an environmentally friendly and simple workup.



Scheme 2. Substrate scope under standard conditions in water.

Considering the broad applications of these sulfoximines as biologically and medicinally active compounds for improved

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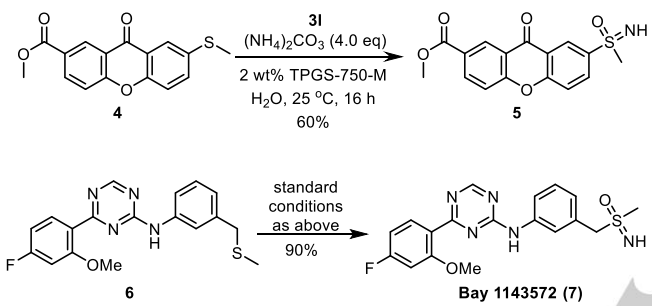
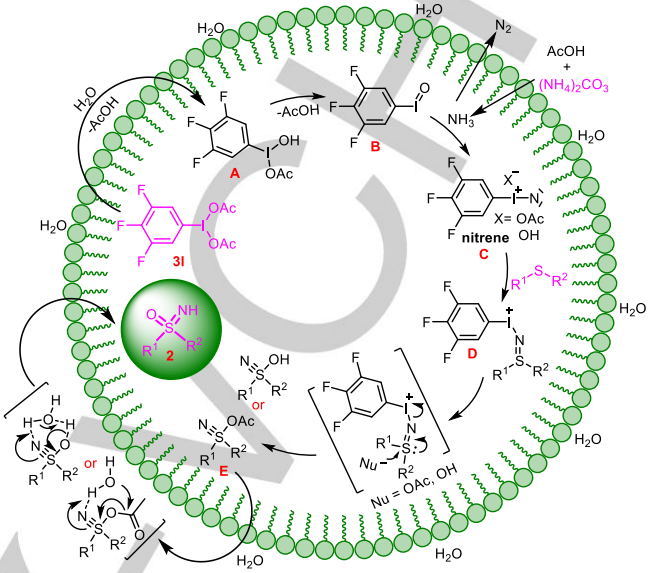
solubility and oral bioavailability over non-sulfoximine analogs, we attempted to apply this method and modify the structure of natural products in order to obtain better physicochemical properties. Xanthones are present in many nature products and is well known for their anti-cancer activities. However, almost all of these compounds raised a solubility concern in most of the solvents.[25] Thus we explored our newly developed procedure for the modification of the xanthones (**4**)[26] bearing a sulfide group. As shown in Scheme 3, The desired product xanthone sulfoximine **5** was synthesized with the newly developed standard conditions in 60% yield, which has shown a good solubility in various solvents. Another application of this methodology is the synthesis of Bay 1143572 (PTEFb Inhibitor, Phase I). In 2018, Reboul reported a 5-step synthesis of Bay 1143572 with a late-stage sulfoximination.[27] Under our method that applies green chemistry, the desired PTEFb inhibitor BAY 1143572 in racemic form was prepared in 90% yield.



Scheme 3. Synthesis of xanthone derivative **5** and Bay 1143572 in water.

The mechanism of the NH-sulfoximination of sulfide or sulfoxide with $PhI(OAc)_2$ in MeOH, trifluoroethanol or other organic solvents has been fully studied and proposed by Reboul, Luisi and Bull group. In these studies, the key intermediates similar to trifluoroiodosylbenzene (**B**), nitrene (**C**) and thiazyne (**E**) have been detected in the reactions via the NMR and HRMS analysis (Scheme 4).[8][9] Based on these pioneering work, a modified reaction mechanism to form NH-sulfoximines in water was proposed in Scheme 4. In the absence of MeOH, water was supposed to participate in the reaction with **3I** to form the trifluoroiodosylbenzene **B**, which then directly reacted with NH_3 to afford the key intermediate nitrene **C**. Apparently, the introduction of the fluorine groups on the benzene ring enhances the rate via its electrophilicity to generate intermediate **A** and initiates the reaction cycle. Then the active nitrene **C** is captured by sulfide to afford the sulfilimine **D**. The formation of **D** was indirectly verified by the reaction of sulfoximine with $PhI(OAc)_2$, which afforded an iodonium salt containing an I-N single bond characterized by Luisi and Bull group.[8b] The nucleophilic attack of an acetate anion or H_2O on **D** delivers the sulfanenitrile intermediate **E**, which was attacked by H_2O to afford the sulfoximines in good yields under mild conditions. Under the surfactant catalysis, the water-promoted aggregation of TPGS-750-M enables the formation of nanomicelles,[17a] which surround water-insoluble organic substrates and provide a facile environment for reactions. As water is supposed to participate in the reaction, the organizational aspects of the formed micelles by placing the water within the PEG region and close to the inner cores also facilitate the essential conversion.[28] During the reactions, the steps that need water may take place outside the micelle inner core to afford the product, which then re-enters to undergo the following conversion. The ammonium carbonate supplying ammonia could be either inside, or out, depending upon its distribution to provide the NH_3.



Scheme 4. Plausible reaction mechanism under aqueous micellar conditions.

In summary, we have developed a green, efficient, and economical method for the synthesis of sulfoximines from sulfides with diacetoxytrifluoroiodobenzene (**3I**) in water. In this protocol, TPGS-750-M was used to enable an NH transfer and oxidation through nanomicelles. The use of ammonium carbonate as the N source ensured a relatively safe condition. Importantly, a newly developed hypervalent iodine (III) reagent can readily oxidize sulfides and afford the corresponding trifluoroiodobenzene, which can be efficiently recovered from the reaction mixture by a simple liquid–liquid biphasic extraction procedure. Moreover, this reaction could be conducted on a gram scale, and has been successfully applied for the synthesis of xanthones derivative **5** and the racemate Bay 1143572. This newly developed synthetic method to prepare the sulfoximines has exemplified many desirable features of green chemistry.

Experimental Section

General procedure for the synthesis of NH-sulfoximines, and recycling of iodoarene and solvents.

To a 10 mL single neck tube was charged with sulfide **1** (0.5 mmol), TPGS-750-M (2% wt, 2 mL), ammonium carbonate (2.0 mmol, 4.0 eq.) at room temperature, and then compound **3I** was added in one portion. The resulting reaction mixture was stirred at 25 °C for 16 h. It was quenched with concentrated aqueous ammonia (35%) (2 mL) and stirred for 10 minutes. hexafluoroisopropanol (1 mL) was added if sulfoximines shown a little low solubility. The resulting mixture was extracted sequentially with *n*-heptane (10 mL × 3) and CH_2Cl_2 (5 mL × 3) to separate the 1,2,3-trifluoro-5-iodobenzene and sulfoximines **2**, respectively. The two combined organic layers were dried over anhydrous $MgSO_4$ and distilled under atmospheric pressure to recycle the organic solvents, CH_2Cl_2 and *n*-heptane. The product **2** was further purified by column chromatography

using silica gel as stationary phase and mixtures of pentane/ethyl acetate or dichloromethane/methanol as eluent.

Acknowledgements

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Keywords: Sulfoximines • Surfactant • Green chemistry • Oxidation • Recyclable

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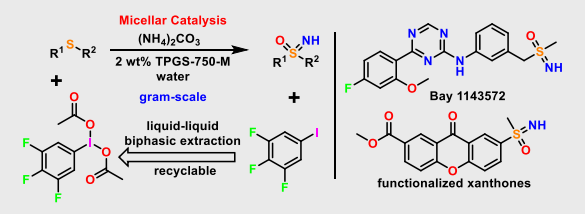

The synthesis of NH-sulfoximines has been first developed in a mild, sustainable conditions in an aqueous solution using surfactant TPGS-750-M catalyst at room temperature. In this newly developed process, convenient recyclable strategy to regenerate the indispensable hypervalent iodine(III) was utilized. This optimized protocol is compatible with a broad range of functional groups and could be easily performed on a gram scale.

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Synthesis of NH-Sulfoximines Using Recyclable Hypervalent Iodine (III) Reagents under Aqueous Micellar Conditions