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# A convenient, mild and green synthesis of NH-sulfoximines in flow reactors

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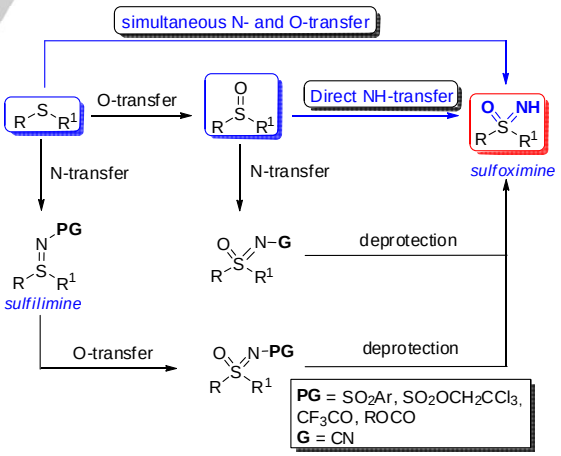
**Abstract:** NH-Sulfoximines are emerging as useful and important targets in drug discovery and synthetic organic chemistry. We report herein the development of an efficient, convenient, and sustainable continuous flow strategy, for the direct straightforward preparation of NH-sulfoximines using sulfides or sulfoxides as suitable starting material. The flow process uses $PhI(OAc)_2$ as the oxidant and aqueous solutions of ammonia as the N-source. The scope of the reaction has been demonstrated by using several substituted sulfides and sulfoxides including enantioenriched and biologically relevant starting materials. The flow strategy was found more convenient with respect to conventional batch processing.

## Introduction

The chemistry of sulfoximines encompass valuable applications spanning from CH-activation or ortho-metallation,[1] to the preparation of sulfurated functionalities,[2] useful as chiral auxiliaries,[3] ligands for asymmetric catalysis,[4] and active ingredients for medicinal chemistry.[5] Neverthless, this mono-aza analogue of sulfone still attracts interest in synthetic organic chemistry and drug discovery. The lack of a comprehensive exploitation of this remarkable class of compounds could be ascribed to their relatively recent discovery, and to hazards associated with older synthetic procedures as well as to the general inapplicability of these methodologies for large-scale productions. Only recently, with the aim to remark the importance of this underrepresented functional group in drug discovery, a number of compounds containing the sulfoximine moiety have been evaluated for medical studies, and several sulfoximines-bearing molecules entered clinical trials.[6] Remarkably, Bayerô researchers evaluated the biological activities of marketed drug analogues, and advanced clinical candidates in which a portion of the molecule was replaced by a sulfoximine functionality.[7] Over the last decade, several methodologies for the preparation of sulfoximines have been introduced, mostly based on the electrophilic transfer of an N-R group to sulfoxides or by a different sequence starting from sulfides. [8] Moreover, for accessing NH-sulfoximines, additional deprotection steps of N-protected sulfoximines would be required (Scheme 1). As for NH-sulfoximines, the availability of a free nitrogen group offers an additional site to introduce molecular diversity, as proved by the development of methodologies such as kinetic resolution,[9] N-trifluoromethylation,[10] trifluoromethylthiolation,[11] aroylation,[12] intramolecular halocyclization,[13] alkynylation,[14] alkylation,[15] and thioetherification.[16] In collaboration with Bullô's group, we recently contributed to the field, by developing convenient metal-free and straightforward protocols for the direct preparation of NH-sulfoximines either starting from sulfoxides or sulfides. [17]




**Scheme 1.** Strategies for accessing NH-sulfoximines.

Given the importance of the NH-sulfoximine functionality, the development of efficient and sustainable strategies, aimed at introducing this structural motif into a molecule, is still a demanding research area. In particular, the development of new, efficient, atom economic, and safe synthetic protocols for the synthesis of NH-sulfoximines, could have impact for industrial applications. In this context, the use of flow chemistry technology, capable to bring about benefits such as enhanced

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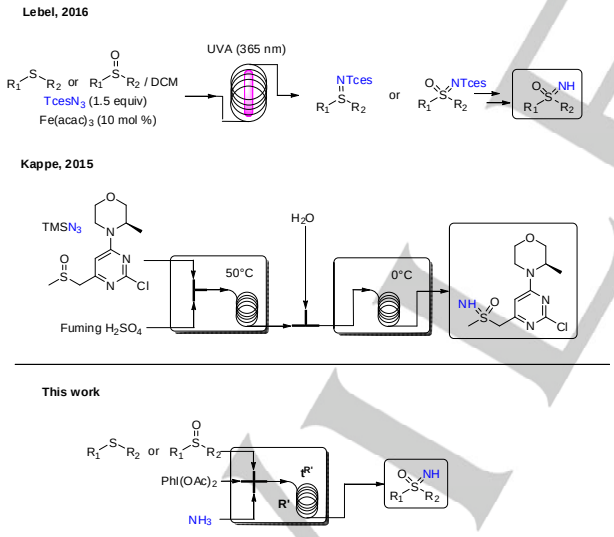
heat and mass transfer, reduced reaction volumes, as well as improved reagent mixing, with respect to conventional batch transformations, should be promoted.[18] In addition, a continuous flow process for the imination of sulfide and/or sulfoxides holds the potential to significantly increase safety and to reduce production costs. To date, only a few processes for the synthesis of sulfoximines have been developed under flow conditions. Lebel and co-workers reported a photochemical process for the synthesis of sulfilimines and sulfoximines by imination of sulfides and sulfoxides respectively. [19] The flow system required a particular photoreactor, in which the solutions of sulfide or sulfoxide reacted with trichloroethoxysulfonyl azide ($TcesN_3$), in the presence of catalytic Fe(III) acetylacetonate, producing in good yields and stereoselectivities aromatic and aliphatic N-Tces substituted sulfilimines or sulfoximines (Scheme 2). This photochemical continuous flow process resulted very efficient, giving protected derivatives within 50-90 min, albeit a quite laborious procedure was employed to remove the Tces group in order to reveal NH-sulfoximines. In another very recent example, Kappe and co-workers, reported a continuous flow protocol for the preparation of a pharmaceutically relevant target molecule by imination of a sulfoxide group. [20] The reaction proceeded under severe conditions by using $TMSN_3$ in a biphasic system, and fuming sulfuric acid at 50 °C (Scheme 2). Kappe's work highlights the potential of the flow technology to significantly increase the safety of this synthesis. However, the protocol focused on the preparation of a single pharmaceutical target rather than on a systematic study on the imination of sulfoxides, and did not preserve the stereochemistry of the starting sulfoxide.

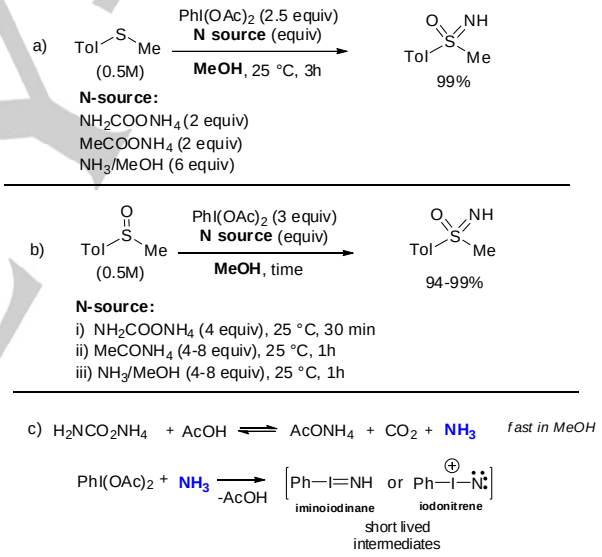



**Scheme 2.**

Building on our previous contribution on the development of more sustainable synthesis of NH-sulfoximines, and on our involvement in the field of flow chemistry, [21] we evaluated the possibility to transfer the direct imination of sulfides and sulfoxides in a flow reactor in order to provide a strategy with more environmental compliance. Herein, we report the development of such safer, metal-free continuous flow protocol for the direct synthesis of NH-sulfoximines using convenient and inexpensive nitrogen sources.

## Results and Discussion

The investigation started considering our previous batch experiments on sulfides and sulfoxides, directly providing NH-sulfoximines, under mild conditions, employing a suitable source of ammonia in the presence of phenyliodo diacetate (Scheme 3). This straightforward metal-free protocol has been tested on several sulfides and sulfoxides, proving robustness and functional groups tolerance. As reported in Scheme 3, several sources of ammonia such as ammonium carbamate, ammonium acetate, and methanol solution of ammonia were found effective either starting from sulfides, or sulfoxides. The reactions could be run in different solvents such as methanol, acetonitrile, and toluene but required a precise stoichiometry and 0.5 M concentration in sulfides or sulfoxide (Scheme 3). Mechanistic study supported the hypothesis that a short-lived iodonitrene or iminoiodinane species are likely responsible for the N-transfer to the sulfur atom (Scheme 3, c).[17b, 22]

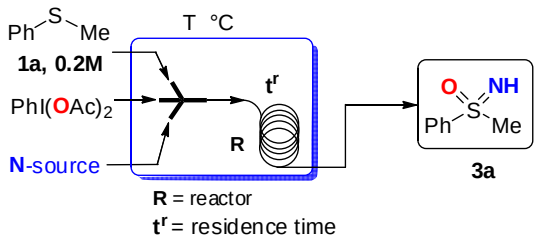



**Scheme 3.**

With the aim to develop a more sustainable and practical protocol for the synthesis of NH-sulfoximines, we planned the experiments in a flow reactor considering: a) the nature of the solvent; b) the most suitable source of ammonia; c) the stoichiometry of the reaction. We reasoned that methanol would have been a suitable solvent, while, as source of ammonia, we considered that the ammonium carbamate would have been problematic to handle under flow conditions (Scheme 3, c), and not very practical because of its intrinsic instability. For these reasons, we focused our attention towards more convenient alternatives such as ammonium acetate and aqueous solution of ammonia. As for the stoichiometry, we aimed at reducing the equivalents of $PhI(OAc)_2$ with respect to batch processing.
From a technical point of view, a Vapourtec R2 system equipped with a 10mL PTFE reactor, and 2 mL PTFE loops was initially used for the optimization study (see Supporting Information).

First, we examined the N- and O-transfer to sulfides. In choosing the best starting point for the flow process, we considered that the high concentration of sulfide (0.5 M), used under batch conditions, would have required high concentrations of both $PhI(OAc)_2$, and N-sources with risk for precipitation and clogging.[23] We found that lowering the molar concentration of methylphenyl sulfide **1a** up to 0.2 M in methanol avoided precipitations or handling of slurries. The results of the optimization study are collected in Table 1.

**Table 1.** Flow oxo- imination of sulfide **1a**: Optimization study.



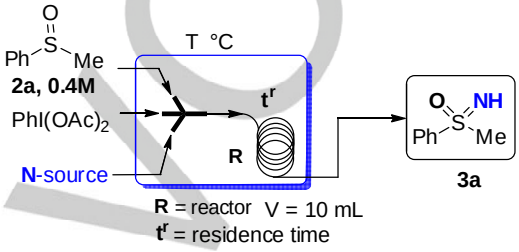

| entry | $PhI(OAc)_2$ (equiv)[b] | N-source (equiv)[b] | T °C | $t^r$ (min) | **3a**[a] (%) |
|---|---|---|---|---|---|
| **1** | **2.5** | **$AcONH_4$ (3)** | **20** | **30** | **97** |
| 2 | 2.5 | $NH_{3(aq)}$ (3) | 20 | 30 | 86 |
| 3 | 2.5 | $NH_4COONH_2$ (3) | 20 | 30 | 99 |
| 4 | 2.5 | $(NH_4)_2CO_3$ (3) | 20 | 30 | 97 |
| 5 | 2.5 | $AcONH_4$ (2) | 20 | 30 | 89 |
| 6 | 2.5 | $NH_{3(aq)}$ (3) | 20 | 15 | 99 |
| 7 | 2.5 | $NH_{3(aq)}$ (3) | 20 | 5 | 95 |
| 8 | 2.5 | $NH_{3(aq)}$ (2) | 20 | 15 | 99 |
| 9 | 2.0 | $NH_{3(aq)}$ (3) | 20 | 15 | 96 |
| 10 | 2.0 | $NH_{3(aq)}$ (2) | 20 | 15 | 60 |
| **11** | **2.0** | **$NH_{3(aq)}$ (2)** | **0** | **15** | **95** |
| 12 | 2.0 | $NH_{3(aq)}$ (2) | 0 | 5 | 58 |

[a] Calculated by $^1H$ NMR of the crude reaction mixture under steady-state conditions. [b] Solution in MeOH.

According to batch procedure, using methanol as the solvent, at 20 °C, and 2.5 equiv of $PhI(OAc)_2$, several N-sources (3 equiv) were compared (Table 1, entries 1-4).[24] We were glad to find that the reaction proceeded in all cases furnishing sulfoximine **3a** in good to excellent yields.[25] For sake of comparison, ammonium carbamate and ammonium carbonate were also evaluated, observing excellent performance (Table 1, entries 4, 5). Nevertheless, handling and dosing of ammonium carbamate was not simple because of its tendency to decompose. In the case of ammonium carbonate, the results proved that this salt could be a suitable cheap source of ammonia, compatible with the reaction conditions. As drawback, $NH_4(CO_3)_2$ dissolves slowly in methanol and the resulting solution need to be filtered before using under flow conditions. For these reasons, we decided to focus our attention on the readily available aqueous solution of ammonia (28%$_{w/w}$) as suitable, cheap, and practical N-source. However, $NH_4OAc$ was also found to be a suitable and convenient N-source but need to be used under the conditions reported in Table 1 (compare entries 1 and 5). In order to improve the performance of the reaction, using $NH_{3(aq)}$ as N-source, the effect of the retention time, the temperature, as well as the stoichiometry were considered (Table 1, entries 6-12). Reducing $PhI(OAc)_2/NH_{3(aq)}$ molar ratio (2:2), and retention time, was detrimental for the yield (Table 1, entry 10). Higher yields were achieved using 2 equiv of $PhI(OAc)_2$, and 3 equiv of $NH_{3(aq)}$ at 15 min residence time (Table 1, entry 9), or by using higher amount of $PhI(OAc)_2$ (Table 1, entries 7, 8). As best compromise, the use of 2 equiv of $PhI(OAc)_2$, 2 equiv of $NH_{3(aq)}$, 15 min of residence time at 0°C furnished sulfoximine **3a** in 95% yield (Table 1, entry 11). It is worth pointing out that such optimized conditions allowed to use a reduced amount of $PhI(OAc)_2$ with respect to batch conditions (2 equiv *vs* 2.5 equiv).

Next, the imination of sulfoxides was considered. Surprisingly, using sulfoxide **2a** as test molecule for the optimization study, it was found that the reaction performed less well with respect to sulfide **1a** (Table 2).

**Table 2.** Flow imination of sulfoxide **2a**: Optimization study.

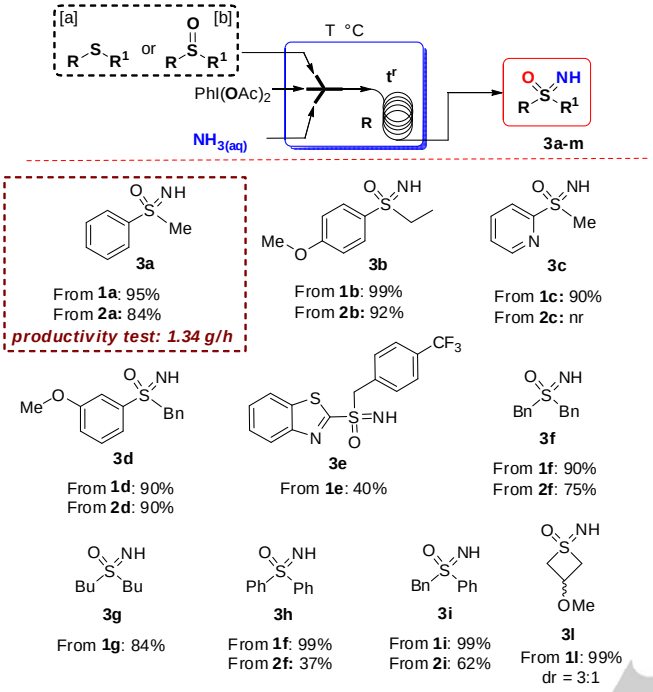



| entry | $PhI(OAc)_2$ (equiv)[b] | N-source (equiv)[b] | T °C | $t^R$ (min) | **3a**[a] (%) |
|---|---|---|---|---|---|
| 1[c] | 2.0 | $NH_{3(aq)}$ (4) | 20 | 30 | 53 |
| 2[c] | 3.0 | $NH_{3(aq)}$ (4) | 20 | 30 | 50 |
| 3 | 2.0 | $NH_{3(aq)}$ (2) | 20 | 30 | 47 |
| **4** | **2.0** | **$NH_{3(aq)}$ (2)** | **0** | **30** | **84** |
| 4 | 2.5 | $NH_{3(aq)}$ (3) | 20 | 30 | 58 |
| 5 | 2.5 | $NH_{3(aq)}$ (4) | 20 | 30 | 53 |
| 6 | 2.5 | $NH_{3(aq)}$ (3) | 50 | 10 | 37 |
| 7 | 2.0 | $AcONH_4$ (2) | 0 | 15 | 65 |
| **8** | **2.0** | **$AcONH_4$ (2)** | **0** | **30** | **80** |
| 9 | 2.0 | $AcONH_4$ (2) | 20 | 30 | 65 |
| 10 | 2.0 | $AcONH_4$ (3) | 0 | 30 | 58 |
| 11 | 2.0 | $AcONH_4$ (3) | 0 | 15 | 46 |

[a] Calculated by $^1H$ NMR of the crude reaction mixture under steady-state conditions. [b] Solution in MeOH. [c] 0.2 M solution of substrate in MeOH.

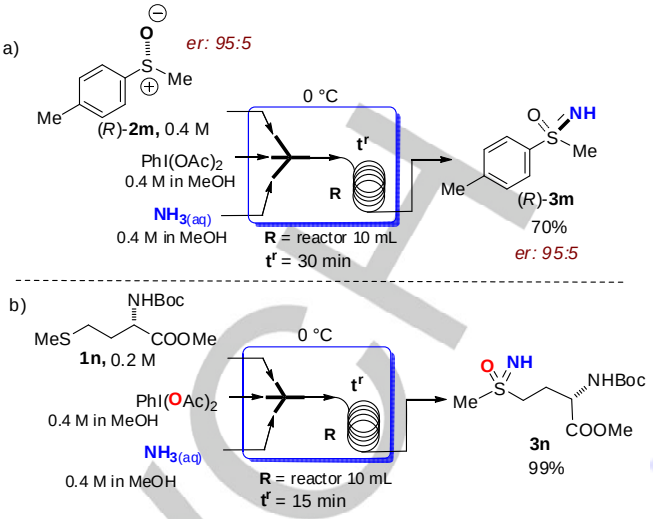
Unfortunately, the use of 0.2M solution of **2a,** 2 or 3 equiv of $PhI(OAc)_2$, and 4 equiv of ammonia, resulted in a low yield of the corresponding sulfoximine **3a** (Table 2, entries 1, 2). According to batch conditions, a higher concentration of sulfoxide is mandatory to speed up the reaction and observe full conversion. Thus, the optimization experiments were executed using a 0.4 M solution of **2a**. Furthermore, in order to handle more concentrate solutions of $PhI(OAc)_2$ and N-source, a different set-up for the flow reactor was considered. In particular, syringe pumps were employed to feed a 10 mL PTFE coil reactor.[25] Both ammonium acetate and aqueous solution of ammonia were employed as N-sources. As reported in Table 2, the reaction performed well at lower temperature (Table 2, compare entries 3, 4 and 6) using 2 equiv of $PhI(OAc)_2$, and 2 equiv of N-sources (Table 2, entries 4 and 8). The results obtained in the imination of sulfoxide showed that, under flow conditions, the stoichiometric ratio between the oxidant and the N-source is an important parameter, as well as the residence time. As reported in Table 2, the use of higher $PhI(OAc)_2$/N-source ratios and shorter residence time were detrimental for the yields (entries 4-6 and 9-11). In the case of sulfoxide **2a**, conditions of entries 4 and 8 (Table 2) were found as the best compromise in terms of stoichiometry of reactants, and yield of the reaction. It is also remarkable that with sulfoxides, the use of a flow reactor allowed to reduce the

amounts of oxidant ($PhI(OAc)_2$) and N-sources, with respect to the batch processing. Another important point is that convenient and easy to handle N-sources could be employed. Taken as whole, the developed flow processes resulted more sustainable starting either from sulfides or from sulfoxides.




**Scheme 4.** Scope of the reaction. [a] Flow conditions: sulfide (0.2 M), 222 μL/min; $PhI(OAc)_2$ (0.4 M), 222 μL/min; $NH_3$(aq) (0.4 M) 222 μL/min; residence time: 15 min; solvent: MeOH; reactor volume 10 mL; temperature 0 °C. [b] Flow conditions: sulfoxide (0.4 M), 67 μL/min; $PhI(OAc)_2$ (0.4 M), 133 μL/min; $NH_3$(aq) (0.4 M) 133 μL/min; residence time: 30 min; solvent: MeOH; reactor volume 10 mL; temperature 0 °C.

The developed flow protocol was applied to representative examples of sulfides and sulfoxides under optimized conditions, reported in Table 1, entry 11 and Table 2, entry 4 respectively. As reported in Scheme 4, sulfoximines **3a-l** could be obtained under continuous flow conditions with good to excellent yields. According to the optimization study, higher yields were observed using sulfides rather than sulfoxides. This flow process tolerates several substituents at the sulfur atom, including alkyls, cycloalkyls, aryls and heteroaromatics. To further benchmark the flow methodology, sulfoximine **3a** was produced in continuous flow conditions from sulfide **1a**, using a flow system consisting of syringe pumps and 10 mL PTFE flow reactor, observing a productivity of 1.34 g/h. Furthermore, we evaluated the imination of enantioenriched sulfoxide (*R*)-**2m** (er: 95:5) obtaining the corresponding sulfoximine (*R*)-**3m** with complete stereocontrol (er: 95:5) in 70% yield (Scheme 5, a). The functional group tolerance observed with sulfides, was tested with the continuous flow synthesis of biologically relevant methionine sulfoximine (MTO) precursor **3n** by simultaneous one pot O- and N-transfer to protected methionine **1n** (Scheme 5, b).




**Scheme 5.** Further application of the flow synthesis of NH-sulfoximines.

## Conclusions

In conclusion a straightforward continuous flow process for the preparation of NH-sulfoximines has been developed. The flow process uses a more convenient stoichiometry for $PhI(OAc)_2$, with respect to batch conditions, and aqueous solution of ammonia as the N-source. The scope of the reaction has been demonstrated by using several substituted sulfides and sulfoxides including an enantioenriched sulfoxide, and the biologically relevant methionine derivative. Both the developed flow strategies were found more convenient with respect to conventional batch processing.

## Acknowledgements

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**Keywords:** NH-Sulfoximines ÅFlow chemistry ÅN-Transfer Å Microtube reactors ÅSulfur derivatives

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[23] Reactions run in batch conditions, turbid solutions were often observed under optimal reaction conditions.
[24] It is worth mentioning that, based on batch optimization study, at least 2 equiv of $PhI(OAc)_2$ were needed to observe full conversion of sulfide, see ref. 17a,b.
[25] See supporting information for comprehensive tables on the optimization study.

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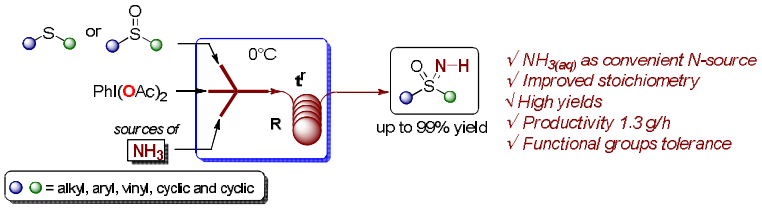


We report herein the development of an efficient, convenient, and sustainable continuous flow strategy for the direct straightforward preparation of NH-sulfoximines starting either from sulfides or from sulfoxides. The flow process uses $PhI(OAc)_2$ as the oxidant and aqueous solutions of ammonia as the N-source. The flow strategy was found more convenient with respect to conventional batch processing.

**NH-Sulfoximines flow synthesis**

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***Page No. ï Page No.***

**A convenient, mild and green synthesis of NH-sulfoximines in flow reactors**