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Synthesis of NH-Sulfoximines from Sulfides by Chemoselective One-Pot N- and O-Transfers

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Direct synthesis of NH-sulfoximines from sulfides has been achieved through O and NH transfer in the same reaction, occurring with complete selectivity. The reaction is mediated by bisacetoxyiodobenzene under simple conditions and employs inexpensive N-sources. Preliminary studies indicate that NH-transfer is likely to be first, followed by oxidation, but the reaction proceeds successfully in either order. A wide range of functional groups and biologically relevant compounds are tolerated. The use of $AcO^{15}NH_4$ affords ^{15}N-labeled compounds.

Sulfoximines have recently emerged as interesting motifs for both medicinal and synthetic chemists.[1] Several pharmaceutical firms have started to consider the sulfoximine group in their drug-discovery programs.[2] Examples of this interest are the pan-CDK inhibitor BAY 1000394 from Bayer,[3] and the ATR inhibitor AZD6738 from Astra-Zeneca[4] (Figure 1), both developed for cancer therapy. Additional examples of biologically active molecules bearing the sulfoximine moiety are collected in Figure 1.[5] Moreover, sulfoximines are also employed as ligands and auxiliaries for asymmetric synthesis,[6] and as directing groups in C–H functionalisation.[7]

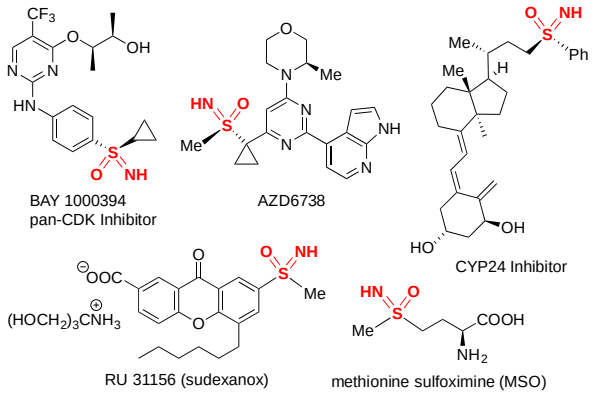

Figure 1. Examples of biologically relevant sulfoximines.

Due to the importance of the sulfoximine group, the development of strategies for sulfoximine incorporation has received considerable attention. Several methods have been introduced in recent years for the preparation of sulfoximines, often based on the electrophilic transfer of an NR group to sulfoxides.[1] With reference to NH-sulfoximines, the availability of a free nitrogen group offers the possibility to further functionalize a molecule. Methodologies for *N*-trifluoromethylation,[8] trifluoromethylthiolation,[9] aroylation,[10] intramolecular halocyclization,[11] alkynylation,[12] and alkylation,[13] have increased the available molecular diversity in compounds bearing the sulfoximine group. Very recently, an interesting preparation of optically active of NH-sulfoximines via organocatalytic kinetic resolution has been reported.[14]

The synthesis of NH-sulfoximines could be accomplished using several strategic approaches (Scheme 1). Arguably, currently the most direct synthesis of NH-sulfoximines involves NH transfer to sulfoxides (Scheme 1, a). Methods to achieve this have involved harsh and explosive or unstable reagents such as azides,[15] O-mesitylenesulfonylhydroxylamine (MSH) or O-(2,4-dinitrophenyl)-hydroxylamine (DPH),[16] and technological advances have been exploited to facilitate use of these reagents.[17] Richards reported the use of DPH with Rh catalysts for the direct preparation of NH-sulfoximines from sulfoxides under mild conditions.[18] We recently reported a new convenient process for direct NH transfer to sulfoxides using

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Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data and copies of ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/x0xx00000x

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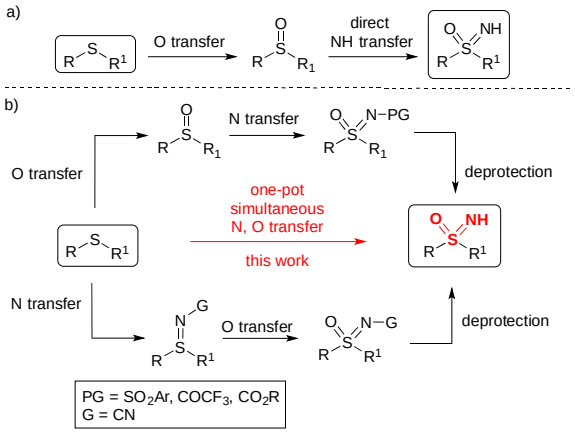
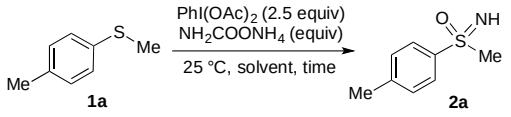
ammonium salts as the source of NH in combination with bisacetoxyiodobenzene ($PhI(OAc)_2$), without requiring a metal catalyst.[19]



Scheme 1. Strategies for the preparation of NH-sulfoximines.

Alternative approaches to NH-sulfoximines are based on multi-step syntheses starting from sulfides (Scheme 1, b). In this case, strategies for a selective N- or O-transfer to the sulfur atom are available, leading to the corresponding sulfilimine or sulfoxide respectively.[20] Two subsequent steps including N- or O-transfer and N-deprotection, would then be required to afford the desired NH-sulfoximine.[21] To date there are no methods to promote selective N- and O- transfer in the same reaction to generate NH-sulfoximines from sulfides, and a convenient method to achieve this would be highly desirable. A previous metal-catalyzed method has been reported by Wirth for preparing N-protected sulfoximines from sulfides.[22] We report herein a direct preparation of NH-sulfoximines from sulfides by using readily available sources of ammonia in the presence of $PhI(OAc)_2$.

We reasoned that our protocol for NH transfer to sulfoxides[19] could be extended to sulfides to generate the corresponding sulfilimines, by reaction with the electrophilic nitrene intermediate. However, we were both surprised and delighted to find that when sulfide **1a** was reacted with 4 equiv of ammonium carbamate (NH_2COONH_4) in the presence of 2.5 equiv of $PhI(OAc)_2$ in MeOH at 25 °C, exclusive formation of the corresponding sulfoximine **2a** was observed (Scheme 2, conditions i). The use of different solvents such as MeCN (Scheme 2, conditions ii) and toluene (conditions iii) resulted again in the formation of **2a**. Using MeOH as the solvent, alternative N-sources were also evaluated. Ammonium acetate (conditions iv) and ammonia in methanol solution (conditions v) were both suitable N-sources to directly convert sulfide **1a** into the corresponding sulfoximine **2a**. The initially expected sulfilimine was not observed under any conditions.

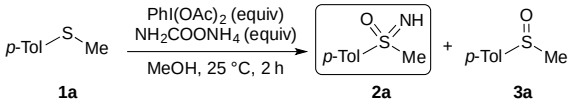


Conditions	Conversion (%)	Yield (%)
i) MeOH, NH_2COONH_4 (4 equiv), 2 h	99	95
ii) MeCN, NH_2COONH_4 (2.5 equiv), 3 h	88	80
iii) toluene, NH_2COONH_4 (2.5 equiv), 16 h	99	95
iv) MeOH, $MeCOONH_4$ (2 equiv), 3 h	99	98
v) MeOH, NH_3/MeOH (6 equiv), 3 h	99	98

Scheme 2. Sulfoximine formation varying solvent and N-source.

With this simultaneous introduction of the two heteroatoms on the sulfur atom occurring in high yield and with complete selectivity, the stoichiometry of reagents employed was optimized. Firstly, the amount of $PhI(OAc)_2$ was considered while maintaining an excess of NH_2COONH_4 (Table 1, entries 1-5). The use of a substoichiometric amount of the oxidant led to sulfoximine **2a** as the main product although with incomplete conversion of sulfide **1a**. Traces of sulfoxide **3a** were also detected. Full conversion was observed with 2 equivalents of $PhI(OAc)_2$ (entry 5). Reducing the amount of NH_2COONH_4 while maintaining an excess of $PhI(OAc)_2$ (entries 6-8), revealed that full conversion could be achieved using only 1 equiv of NH_2COONH_4.

Table 1. Optimization of reagent stoichiometry.



Entry	$PhI(OAc)_2$ (equiv)	NH_2COONH_4 (equiv)	Yield (%)		
			1a[a]	**2a**[a]	**3a**[a]
1	0.3	4	94	6	0
2	0.6	4	75	23	3
3	0.9	4	57	42	1
4	1.5	4	23	76	1
5	2	4	0	97	3
6	2.5	3	0	>99	0
7	2.5	2	0	>99	0
8	2.5	1	0	>99	0

[a] Determined by ^1H NMR analysis of the crude reaction mixture using mesitylene as internal standard.

The data reported in Table 1 suggest that two equivalents of oxidant are mandatory to reach full conversion. Based on our previous mechanistic investigation on the direct NH-transfer to sulfoxides,[19] we reasoned that one equivalent of $PhI(OAc)_2$ would be required to generate the nitrene intermediates (PhI=NH or $PhIN^+$), whereas the second equivalent would promote the oxygen transfer.

To investigate whether N or O is transferred first, we set a series of experiments using diphenyl sulfide derivatives (Scheme 3). Treating diphenylsulfide 1b with the optimised reaction conditions (Table 1, entry 7) gave diphenylsulfoximine 2b in 97% yield (Scheme 3a). It was striking that under these reaction conditions, there was also complete selectivity for the formation of sulfoximine 2b starting from *either* diphenyl sulfoxide 3b, or diphenylsulfilimine 4b, commercially available as the monohydrate (Scheme 3b). These results indicated that the transfer of O and N could occur in either order. From sulfilimine 4b, treatment with $PhI(OAc)_2$ alone, in the absence of an N-source, led to oxidation to the sulfoximine 2b (Scheme 3c). Importantly for the selectivity, reaction of sulfoxide 3b in the absence of the N-source does not further oxidise to the sulfone. On the other hand, reacting the sulfide in the absence of the N-source gave only 13% oxidation to the sulfoxide 3b (Scheme 3d). The addition of 1 equiv water to the same reaction, gave only

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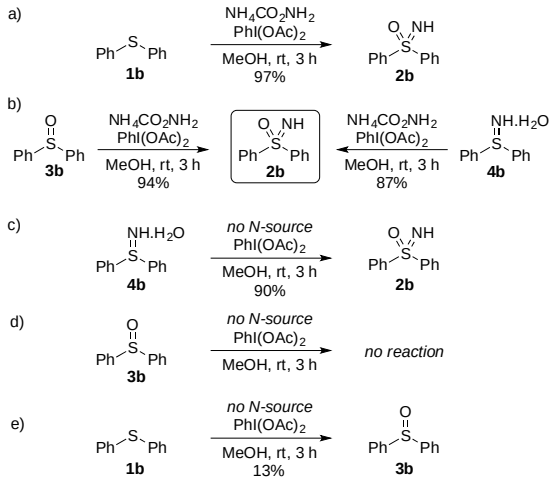
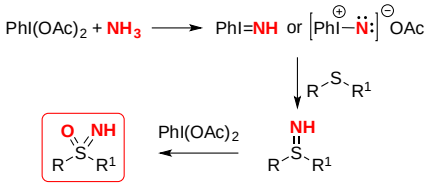
trace sulfoxide, and recovered starting material. For comparison, treatment of sulfide 1a with $PhI(OAc)_2$ in the absence of an N-source gave a higher yield of the sulfoxide (up to 80%), though side products were also observed including Pummerer rearrangement products.[23] When phenylbenzylsulfide (1g in Scheme 5) was reacted with $PhI(OAc)_2$ a complex mixture was obtained containing oxidation and fragmentation/addition products. This contrasts with a 93% yield of the sulfoximine with the added ammonium carbamate (2g, Scheme 5). These preliminary results support the hypothesis that the nitrogen is transferred first and that the corresponding sulfilimine is oxidized to the corresponding sulfoximine by $PhI(OAc)_2$ (Scheme 4).[24]

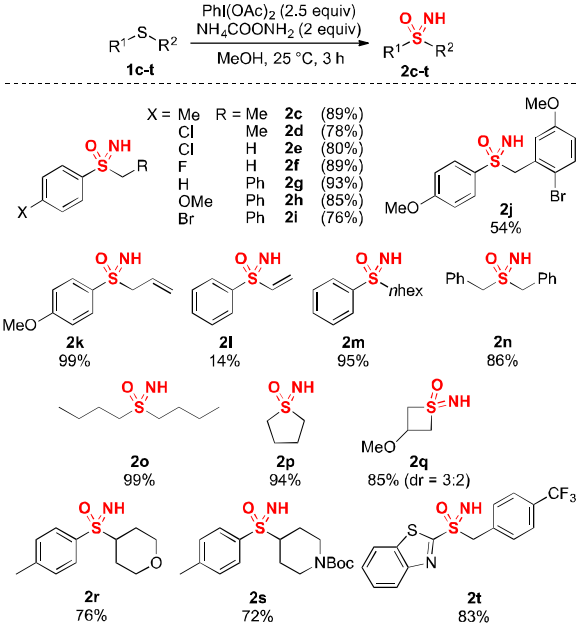


Scheme 3. Consideration of the order of N,O-transfer.



Scheme 4. Proposed reaction sequence.

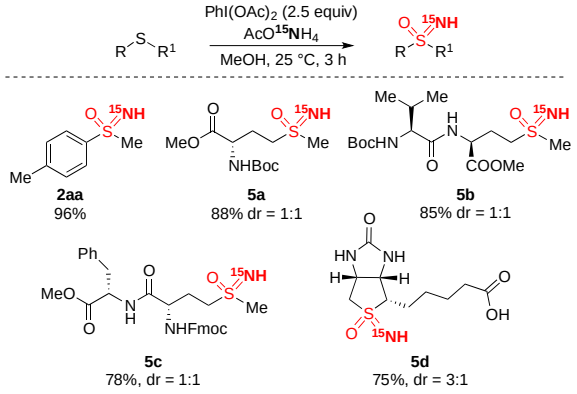
Next, the scope of the reaction was evaluated (Scheme 5). The reaction proceeded well with aryl, alkyl, benzyl and allyl substituted sulfides (**2c-k**, **2m-o**). A low yield was observed when using phenyl vinylsulfide **1l** under various reaction conditions, potentially due to polymerization of the substrate. Cyclic sulfides could be used (**2p**, **2q**) as well as sulfides bearing saturated and aromatic heterocycles (**2r-t**). The protocol was compatible with various functional groups (OMe, CF_3, N-Boc, allyl). However, in the case of $(t\text{-Bu})_2S$ no reaction was observed, presumably due to the high steric demands of the substrate, and only starting sulfide was recovered.



Scheme 5. Reaction scope with various sulfides.

To further validate this method for the direct synthesis of NH-sulfoximines, and to further investigate functional group compatibility, the introduction of a ^{15}N-labeled sulfoximine moiety onto biologically relevant compounds was examined (Scheme 6).

Ammonium acetate was employed as readily available source of ^{15}N, and the protocol was firstly applied to sulfide **1a**. As expected, ^{15}N-labeled sulfoximine **2aa** was obtained in excellent yield and >98% of ^{15}N content (see Supporting Information). As reported in Scheme 6, the reaction could be successfully applied to protected methionine and dipeptides leading to the corresponding sulfoximines **5a-c**. Similarly, biotin could be transformed into the corresponding sulfoximine **5d** without requiring protection of the carboxylic acid group.[25] The corresponding unlabeled sulfoximines reported in Scheme 6 were also obtained by using the standard protocol.



Scheme 6. Preparation of ^{15}N-labeled sulfoximines.

In conclusion, this work reports the first direct synthesis of NH-sulfoximines from sulfides. The protocol uses readily available nitrogen sources in the presence of $PhI(OAc)_2$ as the oxidant,

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which results in highly chemoselective transfer of N and O groups. The reaction tolerates varied sulfur substituents and functional groups. The developed strategy also allowed the ^{15}N-labeling of NH-sulfoximines. Preliminary mechanistic investigations suggest the introduction of the nitrogen followed by the oxidation of the resulting sulfilimine.

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24 While the transfer of NH first appears most likely, we cannot rule out the possibility that the presence of the ammonia source could activate the oxidation reagent and accelerate that pathway. Given that both the sulfoxide and the sulfilimine proceed to the sulfoximine product under the reaction conditions, it is possible that both routes may operate, depending on the substrate structure.

25 The approximate diastereomeric ratios of compounds whereby formation of the sulfoximine gave two stereoisomers (examples **5a-d**, and **2q**) were ascertained by using ^{1}H, ^{13}C and 2D NMR experiments. The relative stereochemistry has not been determined, and NOESY studies on **5d**, which displayed low stereoselectivity in the reaction were inconclusive.

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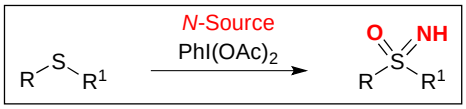
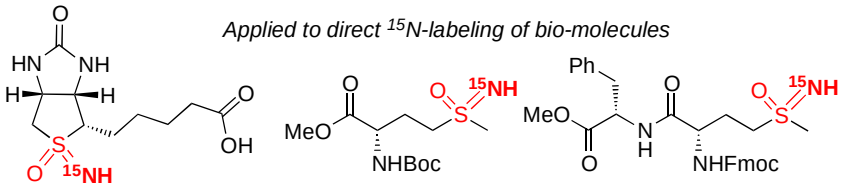


- One-pot direct **N**, **O** transfer
- Wide scope
- Functional group tolerant
- High yields

N-Source: NH_4COONH_2, $AcONH_4$, NH_3

Applied to direct ^{15}N-labeling of bio-molecules



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