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A New, Practical One-Pot Synthesis of Unprotected Sulfonimidamides by Transfer of Electrophilic NH to Sulfinamides

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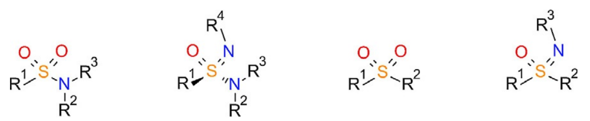
Abstract: Unprotected tertiary sulfonimidamides have been prepared in good to excellent yields in a one-pot transformation from tertiary sulfinamides through NH transfer. The reaction is mediated by commercially available (diacetoxyiodo)benzene and ammonium carbamate in methanol under convenient conditions. A wide range of functional groups are tolerated and initial results indicate that the NH transfer is stereospecific. A small molecule X-ray analysis of NH sulfonimidamide **2a** and its behavior in selected in vitro assays in comparison to the matched sulfonamide are also reported. This new reaction provides a safe, short and efficient approach to sulfonimidamides, which have been the subject of recent, growing interest in the life sciences.

Introduction

The sulfonamide group **1** (Figure 1) has long been a very important pharmacophore in drug discovery, being widely used in anticancer, anti-inflammatory and antiviral agents.[1] In contrast, sulfonimidamides **2**, the mono-aza analogues of sulfonamides, have been rather neglected in the life sciences so far, despite offering very interesting properties such as high stability, favorable physicochemical properties, multiple hydrogen-bond acceptor/donor functionalities and structural diversity, as highlighted recently by Arvidsson and co-workers.[2] Arguably, the use of sulfonimidamides in the life sciences has been hampered by the lack of their commercial availability and the limited methods available for their synthesis.[3] The “state of the art“ concerning sulfonimidamides in drug discovery resembles that of sulfoximines **4**,[4] the mono-aza analogues of sulfones **3** (Figure 1), about 15 years ago.



1 2 3 4

Figure 1. General structures of sulfonamides **1** (1° R^2, R^3 = H; 2° R^2 = H, $R^3 \neq$ H; 3° $R^2 \neq$ H, $R^3 \neq$ H), sulfonimidamides **2** (1° R^2, R^3 = H; 2° R^2 = H, $R^3 \neq$ H; 3° $R^2 \neq$ H, $R^3 \neq$ H), sulfones **3** and sulfoximines **4**.

After its late discovery in 1949, the sulfoximine group garnered only a very moderate interest in medicinal chemistry for many decades. In recent years, however, interest in sulfoximine chemistry has increased substantially, as evidenced by the development of new and safe methods for the preparation of sulfoximines and the clinical evaluation of at least four novel sulfoximines, the kinase inhibitors roniciclib (BAY 1000394),[5] atuveciclib (BAY 1143572),[6] AZD 6738[7] and BAY 1251152.[8] To the best of our knowledge, a sulfonimidamide candidate has yet to be evaluated in clinical trials; however, there are a few recent examples of sulfonimidamides in medicinal chemistry[2] including an analogue of the clinical anticancer agent tasisulam, with comparable antiproliferative activity against two melanoma cell lines in vitro,[9] and saccharin aza bioisosteres, which are interesting, new scaffolds for drug design[10] (Figure 2).

tasisulam analogue saccharin analogue I saccharin analogue II

Figure 2. Sulfonimidamide-based structure of the analogue of tasisulam and general structures of novel saccharin aza-bioisosteres.

Sulfonimidamides **2** were first synthesized in 1962 by Levchenko and co-workers.[11] Since then, only a few synthetic approaches for the preparation of sulfonimidamides have been

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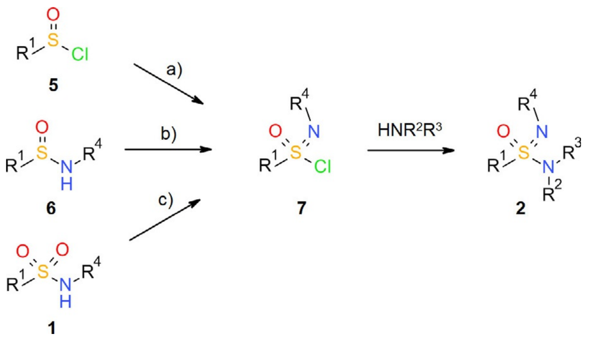
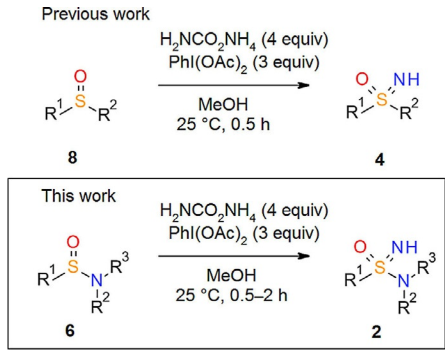


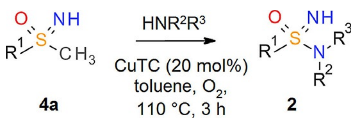
Scheme 1. Common strategy for the synthesis of sulfonimidamides **2** through the reaction of amines with sulfonimidoyl chlorides **7**, which can be prepared by a) oxidative imidation of sulfinyl chlorides **5**, b) oxidative chlorination of sulfinamides **6** or c) deoxychlorination of secondary sulfonamides **1**.



Scheme 3. Synthesis of NH sulfoximines **4** by NH transfer to sulfoxides **8** using ammonium carbamate mediated by the hypervalent iodine reagent $PhI(OAc)_2$, as described by Bull and Luisi,[20] and proposed synthesis of tertiary NH sulfonimidamides **2** ($R^2 \neq H$, $R^3 \neq H$) from tertiary sulfinamides **6** ($R^2 \neq H$, $R^3 \neq H$) by applying similar reaction conditions.

reported, usually involving the nucleophilic substitution of a sulfonimidoyl chloride **7** by an amine (Scheme 1).[12] The required key chloride intermediates **7** have been prepared through different strategies that generally hinge on the oxidative imidation of sulfinyl chlorides **5**,[11,13] oxidative chlorination of sulfinamides **6**[14] or deoxychlorination of secondary sulfonamides **1**.[3,15] However, most of these protocols require the use of a protecting group, and deprotection to the corresponding unprotected NH sulfonimidamides can be challenging. Furthermore, many protocols have a rather limited substrate scope and/or rely on reagents with an associated safety risk, an example being *tert*-butyl hypochlorite, which is commonly used for oxidative chlorination despite its explosive nature.[16]

A new synthetic strategy for unprotected tertiary sulfonimidamides **2**, based on a copper-catalyzed reaction of sulfoximines **4a** with secondary amines, was disclosed by Bolm and co-workers in 2016 (Scheme 2).[17] However, this method requires prior synthesis of the corresponding sulfoximine **4a**, which in our experience can be challenging, depending on the nature of R^1.[18]

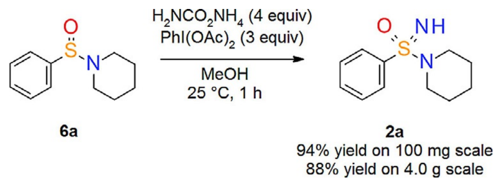


Scheme 2. Redox-neutral S–C to S–N bond-exchange reaction allowing the conversion of sulfoximines **4a** into unprotected tertiary sulfonimidamides **2**; TC = thiophene-2-carboxylate.

During the course of our long-standing interest in sulfoximines in medicinal chemistry,[19] we have witnessed significant improvements over the last 15 years towards safe and efficient synthetic methods for the preparation of sulfoximines. Our attention was captured by a recent report from Luisi, Bull and co-workers outlining the use of a mixture of ammonium carbamate and (diacetoxyiodo)benzene [$PhI(OAc)_2$] for the direct conversion of sulfoxides **8** into NH sulfoximines **4** at room temperature (Scheme 3).[20] Furthermore, this facile and new NH-transfer method was applicable to a wide substrate scope and tolerated a large number of heterocycles and other functionalities.[21] Attracted by the use of commercial reagents and the robust results of this new one-pot method, we were intrigued as to whether these safe reaction conditions could also be useful for the facile synthesis of sulfonimidamides **2** by NH transfer to sulfinamides **6**.

Results and Discussion

Initially, the reported reaction conditions[20] for the imination of sulfoxides **8** were applied to a commercially available tertiary sulfinamide. Thus, 1-(phenylsulfinyl)piperidine (**6a**; 100 mg, 0.48 mmol) was treated with ammonium carbamate (4 equiv) in the presence of $PhI(OAc)_2$ (3 equiv) in methanol at room temperature for 1 hour (Scheme 4). To our delight, the unprotected tertiary sulfonimidamide **2a** was isolated in 94% yield after column chromatography. A scaled-up reaction of sulfinamide **6a** (4.0 g, 19.1 mmol) also resulted in a clean conversion and very good yield (88%). The structure of sulfonimidamide **2a** was confirmed by X-ray analysis (Figure 3).



Scheme 4. Synthesis of tertiary NH sulfonimidamide **2a** by NH transfer to tertiary sulfinamide **6a**.

Given the clean reaction and high yield, we then elected to explore the substrate scope of this new process. Our initial focus was on variation of the NR^2R^3 group of the sulfinamide **6** and thus, tertiary sulfinamides **6a**–**k** were subjected to the standard reaction conditions (Table 1). Gratifyingly, the reactions were generally very clean, resulting in the desired unprotected tertiary sulfonimidamides **2a**–**k** in good to excellent isolated yields. Only the reaction of sulfinamide **6d** (NR^2R^3=N*i*Pr_2)

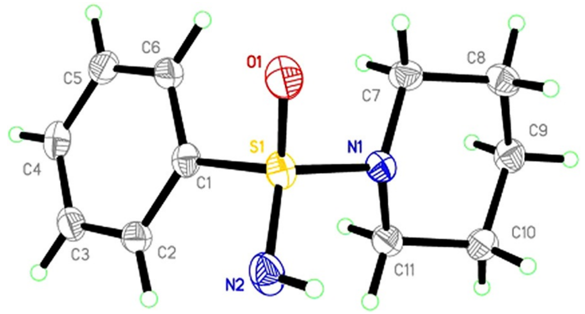
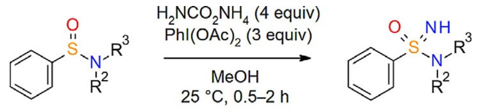
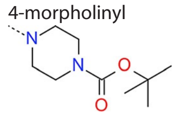
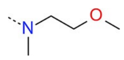
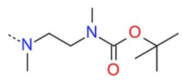
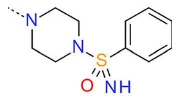


Figure 3. ORTEP plot (50% thermal ellipsoids) of the crystal structure of sulfonimidamide **2a**.

Table 1. Exploration of the substrate scope of the NH transfer reaction: Variation of the NR^2R^3 group in tertiary sulfinamides **6a–k**.



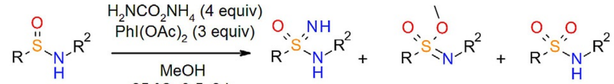
6a–k → **2a–k**

Sulfonimidamide	NR^2R^3	Yield [%][a]
2a	1-piperidinyl	94
2b	NMe_2	72
2c	NEt_2	77
2d	N*i*Pr_2	17
2e	1-azetidinyl	71
2f	1-pyrrolidinyl	77
2g	4-morpholinyl	77
2h		65
2i		67
2j		78
2k[b]		50

[a] Isolated yield. [b] Starting material **6k** = 1,4-bis(phenylsulfinyl)piperazine.

resulted in low conversion, presumably due to steric hindrance of the bulky *N*,*N*-diisopropylamino group, with the tertiary sulfonimidamide **2d** isolated in 17% yield along with recovered starting material. Notably, the reaction of 1,4-bis(phenylsulfinyl)piperazine (**6k**) resulted in a double NH transfer to give the desired product **2k**.

We found, however, that the reaction is limited to the use of tertiary sulfinamides **6**. Subjecting the commercial, primary sulfinamide **6l** to the standard conditions did not result in formation of the corresponding sulfonimidamide **2l**; rather, sulfonimidate **9l** was isolated in 58% yield along with sulfonamide **1l** (15% yield, Scheme 5). Reaction of the secondary ethyl sulfinamide **6m** resulted in a mixture of products from which sulfonimidate **9m** was isolated as the main product. These results are



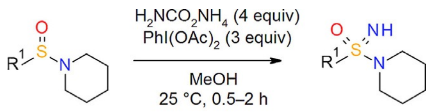
6l: R = 4-MeC_6H_4, R^2 = H; **6m**: R = Ph, R^2 = Et
2l: R = 4-MeC_6H_4, R^2 = H; **2m**: R = Ph, R^2 = Et
9l: R = 4-MeC_6H_4, R^2 = H; **9m**: R = Ph, R^2 = Et
1l: R = 4-MeC_6H_4, R^2 = H; **1m**: R = Ph, R^2 = Et

Scheme 5. Behavior of primary (**6l**) and secondary (**6m**) sulfinamides under the NH transfer reaction conditions.

in line with previous reports of the preparation of sulfonimidates from primary and secondary sulfinamides **6** and hypervalent iodine reagents in the presence of suitable alcohols.[22] The formation of sulfonamides **1** arising from the standard oxidation of sulfinamides **6** is a side reaction under these conditions.

Next, the scope of the R^1 group was explored, with tertiary sulfinamides **6n–y** being additionally subjected to the standard reaction conditions (Table 2). Again, the reactions were very clean, giving the desired unprotected tertiary sulfonimidamides **2n–y** in good to excellent isolated yields. Furthermore, a broad variety of substitution patterns and functional groups common in medicinal chemistry were tolerated. Similar to the reaction of the sterically demanding *N*,*N*-diisopropylbenzenesulfinamide (**6d**, Table 1), only the *ortho*-chloro derivative **6t** (R^1 = 2-ClC_6H_4) resulted in an incomplete but nevertheless clean reaction, providing the tertiary sulfonimidamide **2t** in 29% yield under the standard conditions. However, when the reaction was repeated using an additional portion of $PhI(OAc)_2$ and ammonium carbamate, there was improved conversion which resulted in a 48% isolated yield of **2t**, along with un-

Table 2. Exploration of the substrate scope of the NH transfer reaction: Variation of the R^1 group in tertiary sulfinamides **6n–y**.



6n–y → **2n–y**

Sulfonimidamide	R^1	Yield [%][a]
2a	Ph	94
2n	4-MeOC_6H_4	87
2o	4-FC_6H_4	89
2p	4-$O_2NC_6H_4$	62
2q	3-$F_3CC_6H_4$	81
2r	4-MeC_6H_4	95
2r*	4-MeC_6H_4	88 (48% *ee*[b])
2s	3-ClC_6H_4	85
2t	2-ClC_6H_4	29 (48)[c]
2u	2-pyridyl	85
2v	3-pyridyl	53
2w	cyclohexyl	88
2x	*i*Pr	70
2y	*t*Bu	83

[a] Isolated yield. [b] *ee* determined by chiral-phase HPLC analysis; **2r*** obtained from starting material **6r*** with 51% *ee*. [c] Additional ammonium carbamate and $PhI(OAc)_2$ were used.

reacted starting material. To our delight, sulfinamides with pyridyl or alkyl substituents also reacted successfully to give the corresponding sulfonimidamides **2u–y** in very good yields, illustrating the broad substrate scope of this new, mild reaction. As an initial insight into the stereospecificity of this process, the optically enriched sulfinamide **6r***, which had been prepared with 51% *ee* using the commercial Andersen reagent,[23] was subjected to the standard reaction conditions. The NH transfer proceeded stereospecifically to provide product **2r*** with 48% *ee*.

In a preliminary assessment of the medicinal chemistry properties of sulfonimidamides, the behavior of the fragment-like sulfonimidamide **2a** compared to the matched sulfonamide analogue **1a** in selected in vitro assays was undertaken (Table 3). Considering that our major concern was a possible inherent instability of the sulfonimidamide group, the hydrolytic stability of the two compounds at five different pH values was investigated, along with the metabolic stability in liver microsomes (human, rat and mouse) and also rat hepatocytes in vitro. Furthermore, the Caco2 permeability and log*D* values were determined. In line with our expectations, sulfonamide **1a** displayed a high hydrolytic stability after 24 hours with stirring in media with pH values ranging from 2.0–7.4 (Table 3). Moderate hydrolytic stability was evident at pH 8.0, with 67% recovered test compound. However, sulfonimidamide **2a** also has a very high hydrolytic stability, with 100% recovered test compound after 24 hours with stirring at all tested pH values. In vitro pharmacokinetic studies with sulfonamide **1a** revealed a moderate metabolic stability in human liver microsomes, resulting in a moderate predicted blood clearance (CL_b) of 0.41 $L\,h^{-1}\,kg^{-1}$; however, a low metabolic stability and high predicted blood clearance of sulfonamide **1a** was evident both in rat and mouse liver microsomes [CL_b = 3.8 $L\,h^{-1}\,kg^{-1}$ (rat), 4.0 $L\,h^{-1}\,kg^{-1}$ (mouse)]. A high blood clearance (4.0 $L\,h^{-1}\,kg^{-1}$) was also predicted from in vitro studies with rat hepatocytes. The main sites of metabolism were not determined in these studies. In comparison, the matched sulfonimidamide **2a** revealed a trend for higher metabolic stabilities in vitro: studies with human and mouse liver microsomes resulted in low predicted blood clearances of 0.04 and 1.1 $L\,h^{-1}\,kg^{-1}$, respectively. Sulfonimidamide **2a** exhibited a low metabolic stability in rat preparations, with correspondingly high predicted CL_b values [3.0 $L\,h^{-1}\,kg^{-1}$ (rat liver microsomes), 3.6 $L\,h^{-1}\,kg^{-1}$ (rat hepatocytes)]; however, these data also revealed a trend in rats for a higher metabolic stability of sulfonimidamide **2a** relative to sulfonamide **1a**. In the Caco2 screening assay, sulfonamide **1a** and the matched sulfonimidamide **2a** both had high permeability coefficients (P_{app} A–B) of 393 and 378 $nm\,s^{-1}$, respectively, and no evidence of efflux. However, the switch from the sulfonamide to the sulfonimidamide results in a remarkable decrease in lipophilicity, with a log*D* value of 2.6 (**1a**) compared to 1.9 (**2a**).

Table 3. Comparison of the in vitro properties of sulfonamide **1a** and NH sulfonimidamide **2a**.

Compound	Recovery [%][a] (pH)	CL_b[b] [h/r/m]-LMs [$L\,h^{-1}\,kg^{-1}$]	CL_b[b] rHep [$L\,h^{-1}\,kg^{-1}$]	P_{app} A–B[c] [$nm\,s^{-1}$]	Efflux ratio[c]	log*D* pH 7.5[d]
 1a	91 (2.0) 85 (4.5) 100 (6.5) 100 (7.4) 67 (8.0)	0.41 (h) 3.8 (r) 4.0 (m)	4.0	393	0.64	2.6
 2a	100 (2.0) 100 (4.5) 100 (6.5) 100 (7.4) 100 (8.0)	0.04 (h) 3.0 (r) 1.1 (m)	3.6	378	0.59	1.9

[a] Hydrolytic stability measured as recovery of test compound after 24 hours with stirring at pH 2.0 (citrate buffer), pH 4.5 (citrate buffer), pH 6.5 (phosphate-buffered saline), pH 7.4 (phosphate-buffered saline), and pH 8.0 (sodium borate buffer).[24] [b] Predicted hepatic metabolic clearance based on a high-throughput metabolic stability assay using i) pooled human liver microsomes (hLMs), ii) pooled rat liver microsomes (rLMs), iii) pooled mouse liver microsomes (mLMs), and iv) freshly harvested rat hepatocytes (rHep).[25] [c] P_{app} A–B (apical to basolateral) and efflux ratio (ER) data were generated in a bidirectionally performed Caco2 permeability assay in a 24-well format; ER was calculated as P_{app} B–A/P_{app} A–B.[25] [d] Determined by reversed-phase HPLC.[26]

Conclusion

We have utilized electrophilic NH transfer to achieve the first direct synthesis of tertiary NH sulfonimidamides **2** from tertiary sulfinamides **6**. The developed protocol relies on the readily available nitrogen source ammonium carbamate and the oxidant $PhI(OAc)_2$, and is compatible with a broad substrate scope, providing the corresponding sulfonimidamides **2** in good to excellent yields. Initial results indicate that this reaction process is stereospecific; additional investigations are currently underway. In vitro studies of the properties relevant to medicinal chemistry for compound **2a** have not revealed any intrinsic flaw of the sulfonimidamide group with respect to its application as a new and versatile pharmacophore in the life sciences.

Experimental Section

General synthetic procedure for sulfonimidamides 2

To the sulfinamide (0.48 mmol, 1.00 equiv) were added (diacetoxyiodo)benzene (1.43 mmol, 3.00 equiv), ammonium carbamate (1.91 mmol, 4.00 equiv) and finally MeOH (0.96 mL, 0.5 M). The mixture was stirred in an open flask at RT for 0.5–2 h. When all the starting material had been consumed (as monitored by TLC and UPLC-MS), saturated aqueous $NaHCO_3$ solution and EtOAc were added, and the mixture was stirred for 5 min. The organic layer was separated and the aqueous layer was extracted with EtOAc (3×). The organic phases were combined, washed with brine (3×) and dried over water-repellent filter paper. The volatiles were removed under reduced pressure and the crude product was purified by flash column chromatography.

1-(*S*-Phenylsulfonimidoyl)piperidine (2a)

Prepared according to the general procedure, from commercial 1-(phenylsulfinyl)piperidine (Sigma–Aldrich); crude purified by flash column chromatography (KP-Sil, 0–40% EtOAc in hexane) to give **2a** as a yellow-orange solid (105 mg, 94%): m.p. 99–100 °C; ^{1}H NMR (600 MHz, [D$_6$]DMSO): $\delta = 7.79$–7.74 (m, 2H), 7.66–7.61 (m, 1H), 7.60–7.55 (m, 2H), 4.29 (s, 1H), 2.91–2.74 (m, 4H), 1.56–1.44 (m, 4H), 1.30 ppm (q, $J = 5.82$ Hz, 2H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): $\delta = 136.6$, 132.0, 128.7, 127.7, 47.4, 25.2, 23.2 ppm; IR (KBr): $\tilde{\nu} = 3234$, 2989, 2933, 2837, 1445, 1256, 907, 721, 687, 575 cm^{-1}; HRMS (ESI-TOF) *m/z* [*M*+H]$^+$ calcd for $C_{11}H_{17}N_2OS$: 225.1062, found: 225.1066.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: drug design · hypervalent iodine · medicinal chemistry · sulfinamides · sulfonimidamides

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