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Complementary strategies for synthesis of sulfinamides from sulfur-based feedstock†

Miloš Jabczun, Vladimír Nosek and Jiří Mišek *

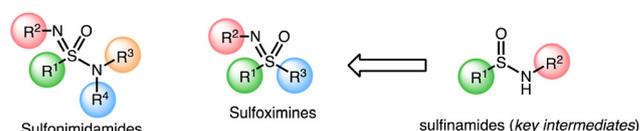
We describe a straightforward one-pot reductive protocol for the synthesis of sulfinamides from sulfonyl chlorides. This method enables the preparation of sulfinamides with a broad range of functional groups. Furthermore, we have expanded a known oxidative pathway to sulfinamides starting from thiols. These methods together provide a general strategy for the synthesis of sulfinamides from common sulfur-based feedstock that is available with large structural and functional group diversity.

Introduction

Sulfinamides have become a valuable chiral auxiliary in asymmetric organic synthesis, and the efficient chirality transfer has also been utilized in the catalytic format.^{1–3} However, sulfinamides are also very useful intermediates in the preparation of sulfoximines and sulfonimidamides that are gaining popularity in medicinal chemistry.^{4–17} The development of efficient synthetic methods for this kind of hexavalent sulfur compound will enable further exploration of this underexplored chemotype. Sulfoximines and sulfonimidamides offer a unique 3D scaffold for the display of three different substituents around the central tetrahedral sulfur atom (Fig. 1). In order to fully utilize these compounds in drug discovery, a mild and general method that allows a straightforward installation of a diverse set of substituents with a variety of functional groups is essential. Sulfinamides provide a key intermediate with *C*- and *N*-substituents as places for diversification.

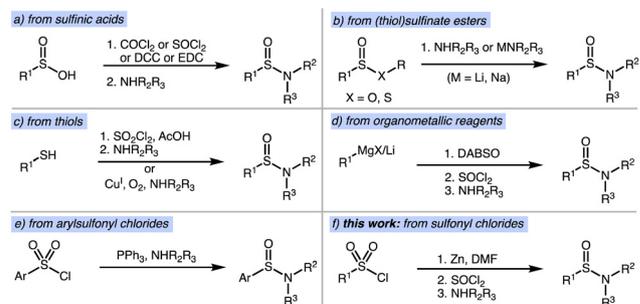
Sulfinamides are commonly synthesized from sulfinic acids by conversion to chloride and subsequent reaction with an amine (Scheme 1).^{18–20} DCC and EDC reagents can also be used for activation of sulfinic acids.^{21,22} However, sulfinic acids are not widely available due to the limited stability caused by possible disproportionation.^{23–25} Another way of making sulfinamides is from starting sulfinate or thioisulfinate esters, which can undergo aminolysis with amines or metal amides.^{26–29} These starting materials are commonly prepared from, again, sulfinic acids or disulfides.^{30–32} Thiols can be converted to sulfinamides in a one-pot format using SO₂Cl₂ and acetic acid to obtain sulfinyl chlorides that react with the

corresponding amine.³³ Copper/palladium-catalysed oxidative transformation of thiols to sulfinamides has also been reported.^{34,35} Alternatively, metal-catalyzed transsulfinamidation can be utilized for diversification of the sulfinamide pool.^{36,37} An elegant approach to sulfinamide synthesis was recently reported by Willis *et al.* The authors utilized sulfur dioxide surrogate DABSO in reaction with organomagnesium/lithium compounds to generate a sulfinate that is further converted to sulfinamide.³⁸ Similarly, arylboron compounds have been reported as a starting material for one-pot reaction leading to sulfinamides.^{39,40} An interesting approach was developed by Harmata *et al.* by utilization of sulfonyl chlorides



- Underexplored chemotypes in drug discovery
- 3D display of up to four substituents

Fig. 1 Structures of underexplored sulfur-based chemotypes.



Scheme 1 Selected one-pot protocols for the synthesis of sulfinamides.

Department of Organic Chemistry, Faculty of Science, Charles University in Prague, Hlavova 2030/8, 12843 Prague 2, Czech Republic. E-mail: misek@natur.cuni.cz

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as a starting material.⁴¹ *In situ* reduction of sulfonyl chloride by PPh₃ provides an intermediate that reacts directly with amines to provide sulfenamides. This method was further improved by using a MOF catalyst.⁴² However, the method suffers from limited substrate scope as only certain aromatic sulfonyl chlorides afford the desired sulfenamides in a reasonable yield. Sulfonyl chlorides, however, represent a common chemical feedstock, and thousands of sulfonyl chlorides with a variety of substitution patterns and functional groups are now commercially available. Therefore, they represent a good starting material for the diversification of sulfenamides at the *C*-substituent. Sulfonyl chlorides can be reduced to sulfinate salt, most commonly by zinc powder or sodium sulfite.^{43–46}

We wanted to explore if sulfonyl chlorides can be utilized for the straightforward, efficient, and general synthesis of sulfenamides. Thiols represent another sulfur-based feedstock that is available with diverse structural and functional group features and can be converted to sulfinyl chloride through above mentioned oxidation with SO₂Cl₂ and acetic acid and further to sulfenamides.³³ Our goal was to explore this oxidative approach as a complementary strategy to the reductive pathway with sulfonyl chlorides and to broaden the structural and functional group diversity of the corresponding sulfenamides. Ultimately, we wanted to show that sulfenamides with structurally diverse *C*-substituents can be converted to sulfonimidamides and thus allow preparation of libraries of compounds from the broadly available feedstock.

Here, we report on two methods that use optimized reductive and oxidative conditions for the preparation of sulfenamides from sulfonyl chlorides and thiols. The direct protocols use a one-pot format without any isolation of intermediates and allow efficient synthesis of sulfenamides with a broad spectrum of functional groups.

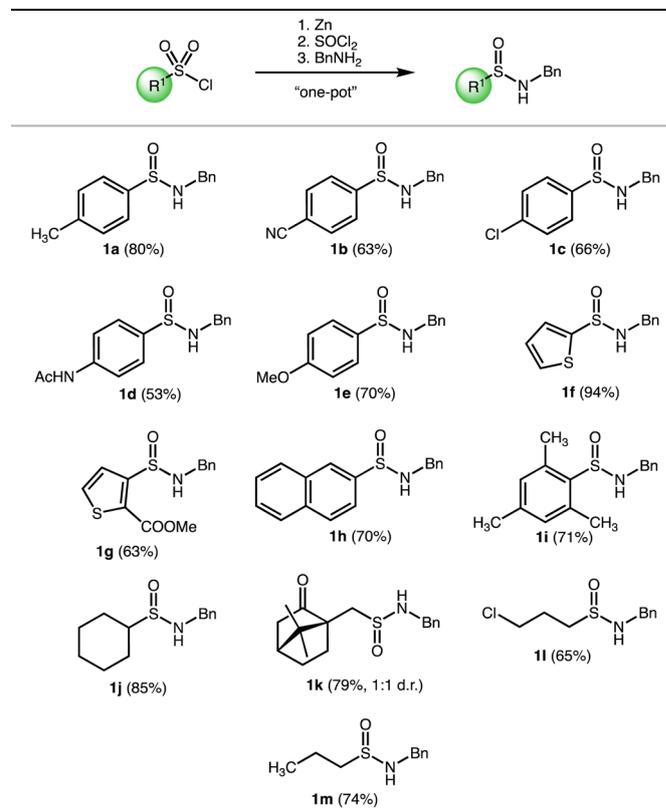
Results and discussion

Our reductive synthetic strategy relies on the fact that sulfinate salts can be easily converted to sulfinyl chlorides that readily react with amines forming sulfenamides. This reaction sequence can be performed in a one-pot protocol. Therefore, a key step is the efficient reduction of sulfonyl chloride to a sulfinate salt. This reduction is usually carried out using sodium sulfite or zinc powder in an aqueous environment. Despite these reductions can form the desired sulfenates with high yields, the aqueous conditions prevent performing the entire desired reaction sequence *in situ* as the subsequent generation of sulfinyl chloride would not be compatible. The sulfenates can be isolated; however, our goal was to devise a direct method without any isolation of intermediates. Moreover, some zinc sulfenates are known to crystallize as hydrates, which could also complicate the preparation of chlorides.⁴⁵ Therefore, we turn to a zinc-based non-aqueous reduction of sulfonyl chlorides. Toluenesulfonyl chloride (TsCl) and benzylamine were used for a model reaction. Reduction of TsCl with a zinc powder in organic solvents was not very efficient,

however in agreement with the literature, we observed that the addition of 1.5 equiv. of DMF in chlorinated solvents significantly improved the yield of the desired sulfinate.⁴⁷ Therefore, these conditions have been utilized for the reaction sequence. TsCl was reduced with zinc powder, the resulting mixture was filtered, rotavaped and the residues dissolved in THF and reacted with SOCl₂. Subsequent addition of benzylamine (1.5 equiv.) with Et₃N (1.5 equiv.) provided the desired sulfinate. Optimization of the individual steps of the sequence resulted in conditions providing sulfinate **1a** in 80% isolated yield (Table 1).

Having the optimized procedure in hands, we proceeded to determine the scope of the synthetic method with respect to the starting sulfonyl chlorides. Satisfyingly, the method is mild enough to tolerate a broad range of functional groups. In general, both (het)aryl and alkyl sulfonyl chlorides were suitable substrates with moderate to good yields (Table 1). Importantly, functional groups that can be attached to sulfenamides at the *C*-substituent include secondary amide (**1d**), cyano group (**1b**), ester (**1g**), ketone (**1k**) and alkyl chloride (**1l**). Thiophene-containing sulfonyl chlorides can be converted to sulfenamides (**1f** and **1g**) as well. Also, sterically hindered

Table 1 Reductive synthesis of sulfenamides^a



^a Reaction conditions: RSO₂Cl (0.81 mmol, 1 equiv.), DMF (1.22 mmol, 1.5 equiv.), Zn powder (0.89 mmol, 1.1 equiv.), DCM, reflux, 1 h, then SOCl₂ (1.63 mmol, 2.0 equiv.) THF, -40 °C, 45 min followed by Et₃N (1.22 mmol, 1.5 equiv.) and benzylamine (1.22 mmol, 1.5 equiv.), rt, on.



mesityl sulfonyl chloride was a good substrate providing the desired product **1i** in 71% yield. Out of the tested functional groups, the nitro group turned out to be incompatible with the method as it gets partially reduced under the reaction conditions. Also, N-heterocyclic substrates provided a complex mixture of products.

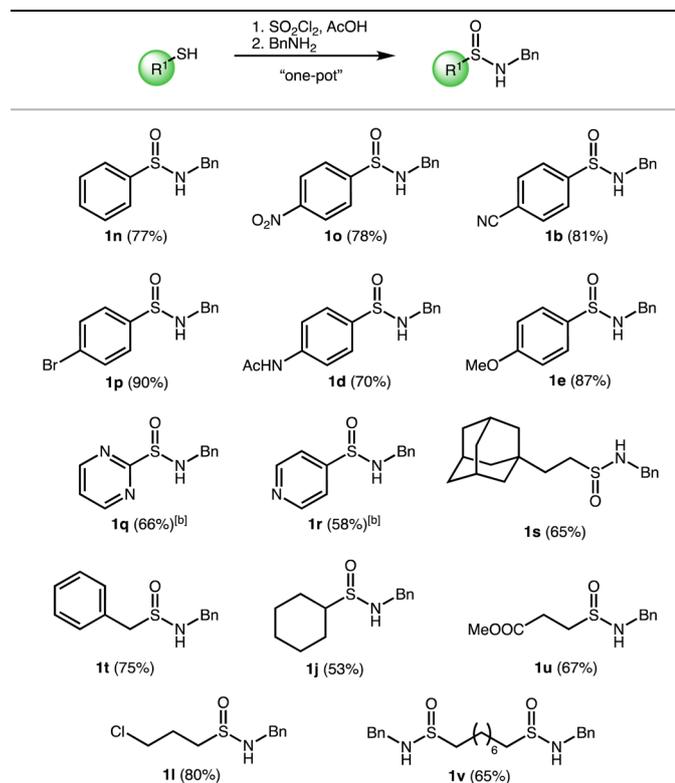
Next, we turned our attention to the oxidative pathway starting from thiols. Conversion of thiols to sulfinyl chlorides and subsequently to sulfinamides was described previously on a small number of substrates.³³ We wanted to explore the substrate scope in comparison to our reductive pathway. One-pot conversion of thiols to sulfinyl chlorides by SO₂Cl₂ and acetic acid and further to sulfinamides was compatible with a variety of aryl and alkyl substituted substrates with functional groups including ester, nitrile, alkyl chloride, secondary amide as well as a nitro group (Table 2). Interestingly, the original report on the preparation of sulfinyl chlorides from thiols states that secondary amides are not compatible with this method. In our hands, sulfinamide **1d** with a secondary amide was obtained in a good yield (70%). In contrast to the reductive pathway, sulfur-containing heterocycles were not compatible substrates due to the oxidative damage of the heterocycle. Also, it has been previously observed that this method is not suitable for

the preparation of sulfinamides from thiols containing N-heterocycles. Our experiments with pyrimidine-2-thiol indeed failed to produce the corresponding sulfinamide using the standard conditions. However, the detailed investigation of the reaction indicated that the major product of the reaction is sulfenamide instead of sulfinamide. This product was difficult to isolate in a pure form. Therefore, we decided to oxidize this product *in situ* to obtain the desired sulfinamide. Delightfully, the careful addition of 1 equiv. of mCPBA at the end of the reaction led to the isolation of sulfinamide **1q** in 66% yield. Using the same modification, pyridine-containing sulfinamide **1r** was also obtained in 58% yield. Given the importance of N-heterocycles in drug discovery, this modification further broadens the scope of useful products available.

In the following experiments, we showed that in addition to benzylamine, sulfinamides can also be successfully produced with other primary, secondary and (het)aryl amines, which is in agreement with a previous report (Table 3).³⁸ Various primary and secondary amines provided sulfinamides in good yields including sterically demanding *tert*-butylamine. Yields of the products with (het)aryl amines are moderate, however it should be noted that they represent unoptimized reaction conditions. It is not unreasonable to expect that reaction condition optimization, for instance by reversing the order of addition of reagents, could increase the yields, as double sulfonylation of the nucleophilic nitrogen can be suppressed.

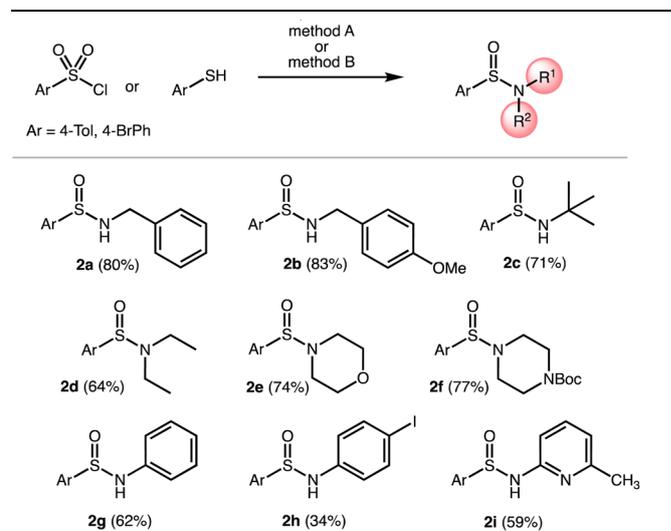
In order to show the utility of the method, we have further converted the sulfinamides to sulfonimidamides.^{38,48} Reaction of sulfinamides with 0.4 equiv. of trichloroisocyanuric acid (TCCA) and subsequent addition of morpholine (1.5 equiv.) provided sulfonimidamides **3a–3i** in good yields (Table 4). This experiment demonstrated that the two complementary methods for the preparation of sulfinamides allow to intro-

Table 2 Oxidative synthesis of sulfinamides^{ab}



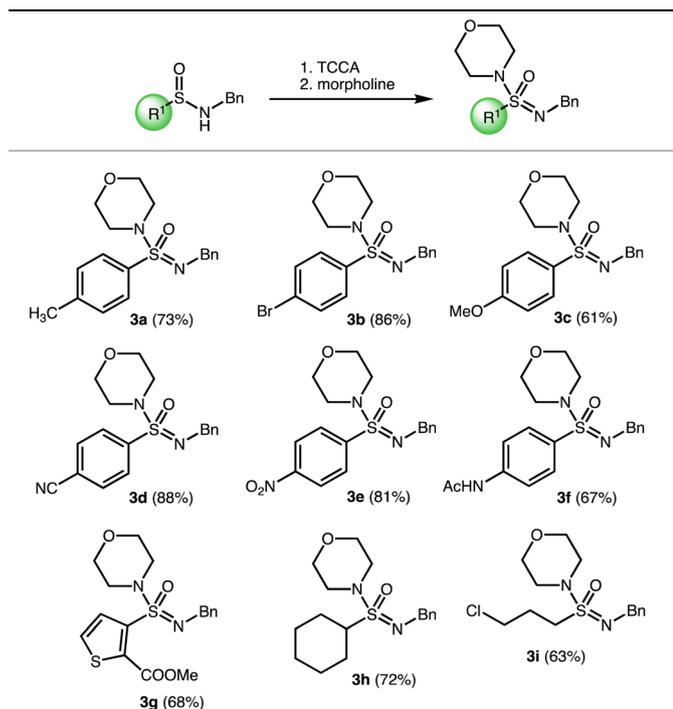
^a Reaction conditions: RSH (1 mmol, 1 equiv.), AcOH (2.1 mmol, 2.1 equiv.), SO₂Cl₂ (3.5 mmol, 3.5 equiv.), THF, rt, 1 h then Et₃N (2.0 mmol, 2 equiv.) and benzylamine (1.55 mmol, 1.55 equiv.), THF, rt, on. ^b The reaction was followed by mCPBA (1 mmol, 1 equiv.), DCM, -40 °C, 30 min.

Table 3 Scope of amine-based nucleophiles^a



^a Reaction conditions: sulfonyl chloride or thiol was converted to sulfinyl chloride by method A or B and reacted with the corresponding amine. For more details see ESI.†



Table 4 Synthesis of sulfonimidamides^a

^a Reaction conditions: sulfonamide (0.16 mmol, 1 equiv.), TCCA (0.06 mmol, 0.4 equiv.), MeCN, rt, 30 min then Et₃N (0.24 mmol, 1.5 equiv.) and morpholine (0.24 mmol, 1.5 equiv.), rt, 60 min.

duce a set of *C*-substituents with high structural and functional group diversity, and this diversity can be transferred to the corresponding sulfonimidamides.

Conclusions

In conclusion, we have developed a new straightforward one-pot protocol for the preparation of sulfonimidamides from sulfonyl chlorides. The method tolerates a broad range of structural features and functional groups. Also, we have tested a complementary oxidative approach to sulfonimidamides starting from thiols. We have shown that the substrate scope for this known method is broader than previously thought and developed a modification for the preparation of *N*-heterocyclic sulfonimidamides. In a broader perspective, when compared to other methods, the reductive pathway enables products with oxidation-sensitive groups (*e.g.*, thiophenes) that are incompatible with oxidative approaches starting from thiols. Also, diverse functional groups (secondary amides, ketones, esters, *etc.*) can be installed in the sulfonamide products, which would be difficult with approaches starting with organometallic reagents. Furthermore, these sulfonimidamides with various functional groups can be efficiently converted to the corresponding sulfonimidamides. Given the structural diversity of commercially available sulfonyl chlorides and thiols, these two complementary methods are set for broad *C*-substituent diversifica-

tion of sulfonamides and sulfonimidamides for discovery chemistry.

Author contributions

M. J. and V. N. designed and performed the experiments and analysed the data. J. M. designed the experiments, analysed the data and wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

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