Sulfonimidates: A versatile intermediate for sulfoximine synthesis *via* C-S bond formation.

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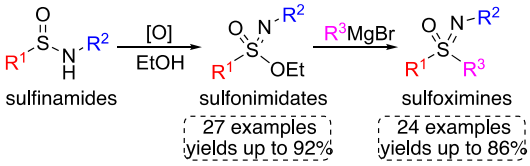
Supporting Information Placeholder



ABSTRACT: The ever-increasing prevalence of sulfoximine derivatives in drug discovery programmes has brought about a renaissance in the development of methods for their synthesis. Sulfoximine synthesis *via* C-S bond formation however has been comparatively underexplored. Herein, we report that sulfonimidates constitute a versatile precursor for the synthesis of medicinally relevant sulfoximines.

In recent years, the synthesis of sulfoximines has drawn considerable interest from academic research groups and pharmaceutical companies alike.[1] The sulfoximine moiety has found success in a number of drug discovery programmes, for example in the ATR inhibitor AZD 6738[1e] and the anti-asthmatic Sudexanox[1f] (Figure 1). As part of our ongoing research programme in the area of organosulfur chemistry, we have been interested in developing novel approaches to the synthesis of valuable sulfur(VI) compounds.[2] Common methods for sulfoximine synthesis[3] largely stem from either the imination of sulfoxides,[4] the oxidation of sulfilimines[5] or directly from sulphides[6] by a dual oxidation/imination protocol (Figure 1a). Each of these approaches however restrict the *N*-substituent on the resultant sulfoximine to those functionalities that can be incorporated into an iminating agent. Consequently, a somewhat step intensive: imination, (often *N*-deprotection) and then *N*-functionalization sequence is commonly employed. To compliment this approach a number of methods for the functionalization of *N*-H sulfoximines have been developed.[7] One alternative strategy for sulfoximine formation is the displacement of a leaving group from a sulfur(VI) derivative with a carbon centred nucleophile. Sulfonimidoyl halides have been trialled for this application, but there are a number of challenges with this approach, for example the organomagnesium mediated reduction of sulfonimidolyl chlorides to sulfinimines.[8a] Recent reports from Sharpless highlight the utility of sulfonimidoyl fluorides for this application, which can be generated in two steps from SOF_4 gas.[9] This is a powerful strategy however the preparation of SOF_4 requires the handling of highly toxic gases at elevated temperature and pressure, a requirement that will likely deter many practitioners. Sulfonimidates on the other hand have only scarcely been employed for the preparation of sulfoximines.

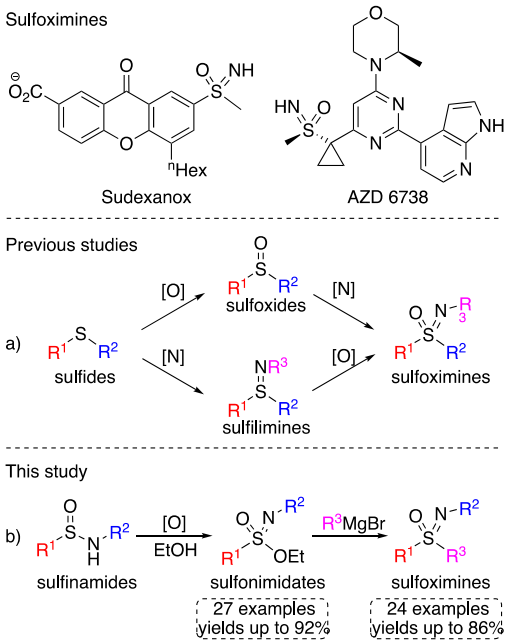


Figure 1. Examples of medicinally relevant sulfoximines (Top); a) Previous approaches to sulfoximine synthesis *via* sulfide oxidation/imination; b) This study: sulfinamides → sulfonimidates → sulfoximines

Our attention was drawn to isolated examples from the early literature[8] where sulfonimidoyl chlorides were initially converted to the corresponding sulfonimidates before reaction with an organometallic reagent to yield sulfoximines. The examples are few and limited to *S*-aryl sulfonimidates; in two instances[8b,c] alkyl lithium reagents are utilised but to the best of our knowledge there is only a single example, reported by Cram where an organomagnesium reagent has been used.[8a] Since these seminal reports, the field of sulfur(VI) chemistry has burgeoned and greatly improved methods for the synthesis of sulfonimidates have been developed,[10] e.g. the oxidative alkoxylation of sulfinamides (Figure 2). In the context of these advances we surmised that a general method for the conversion of sulfonimidates to sulfoximines would offer a powerful and complementary strategy for sulfoximine synthesis.

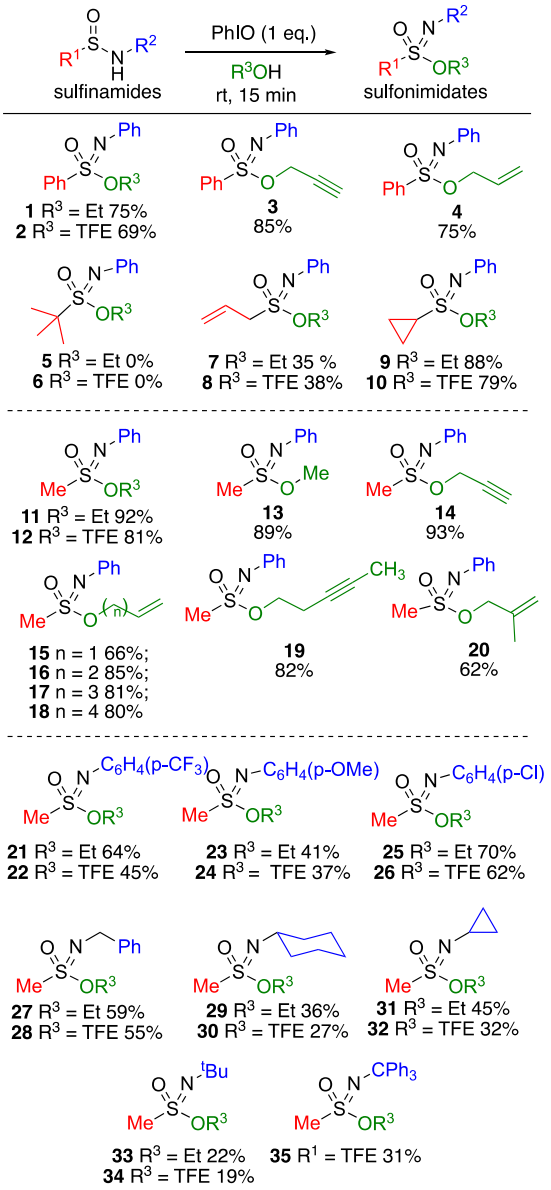
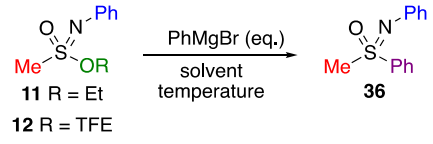


Figure 2. Investigation into the substrate scope of sulfonimidate synthesis *via* iodosylbenzene mediated sulfinamide oxidation. Reactions were performed on a 0.4 -1.9 mmol scale. Yields are for isolated products following chromatography.

Initially, sulfonimidate formation was performed *via* oxidation of the corresponding sulfinamides with iodosylbenzene in the presence of an excess of alcohol as solvent.[10b-d] The oxidation of *N*-phenyl benzenesulfinamide proceeded smoothly both in ethanol and trifluoroethanol, to afford the desired sulfonimidates **1** and **2** in good yields (75% and 69% respectively). As reported by Malacria,[10b-d] bond unsaturations are tolerated under the oxidising reaction conditions; this was confirmed by the formation of *O*-propargyl and *O*-allyl sulfonimidates **3** and **4** (85% and 75% respectively, Figure 2). Previous studies are limited almost exclusively to *S*-phenyl and -tolyl substratates and we were keen to further investigate the scope of this transformation with regard to *S*-substitution. Unfortunately, we were unable to form the *S*-^{t}Bu sulfonimidates **5** or **6** under these conditions, presumably due to steric hindrance. Furthermore, in contrast to the *O*-allyl example **4**, incorporation of *S*-allyl functionality significantly reduced the yield of the transformation (35% and 38% obtained for **7** and **8** respectively). Pleasingly however, the medicinally relevant *S*-cyclopropyl derivatives **9** and **10** could be accessed in 88% and 79% respectively. For the purposes of many drug discovery programmes, low molecular weight fragments are favoured so that screening compounds can be developed that populate "Lipinski space".[11] As such, we were delighted to observe that the highest yields were obtained in the synthesis of *S*-methyl sulfonimidates **11** and **12** (92% and 81% yield respectively). Consequently, we selected *N*-phenyl methanesulfinamide as a test substrate to further investigate the scope of the reaction with regard to the alcohol component. Pleasingly, a range of alkenyl and alkynyl alcohols were incorporated smoothly, affording the corresponding sulfonimidates **13**-**20** in 62-93% (Figure 2). In their proposed role as an intermediate for sulfoximine synthesis however, the "alkoxyl" substituent on the sulfonimidate core would serve as a leaving group so we selected ethanol and trifluoroethanol to screen the scope of sulfonimidate formation with regard to *N*-substitution. Initially the effect of incorporating electron-rich and -poor *N*-aryl substituents was investigated. Pleasingly, *para*-methoxy, -chloro and -trifluomethyl derivatives **21**-**26** could each be obtained in modest to good yield (Figure 2). Next, we moved on to investigate *N*-alkyl substituents.

Table 1. Optimisation of reaction conditions. Reactions were performed on a 0.2-0.5 mmol scale. Yields are for isolated products following chromatography.



Entry	SM	Equiv.	Solvent	T (ºC)	Yield (%)
1	**11**	5 eq.	Et_2O	25	52
2	**11**	5 eq.	Et_2O	-78	55
3	**11**	5 eq.	Toluene	-78	48
4	**11**	5 eq.	THF	-78	65
5	**11**	3 eq.	THF	-78	54
6	**11**	1 eq.	THF	-78	31
7	**11**	5 eq.	THF	-20	59
8	**11**	5 eq.	THF	0	41
9	**12**	5 eq.	THF	-78	42

N-benzyl (**27**/**28**) and *N*-cyclohexyl (**29**/**30**) sulfonimidates were obtained in moderate to good yields (27-59%). Pleasingly, *N*-cyclopropyl, -*tert*-butyl and -trityl sulfonimidates **31**-**35** were also afforded, indicating that bulky groups are considerably better tolerated on the nitrogen substituent than they are on the sulfur (Figure 2). Considering that the best yields for sulfonimidate formation were obtained with *N*-aryl substrates, the *N*-phenyl sulfonimidates **11** and **12** were selected as test substrates to probe sulfoximine formation by Grignard addition (Table 1).

Initially, the reaction was attempted using the conditions reported by Cram,[8a] namely the addition of 5 equiv. of Grignard at 25 °C in Et_2O. Under these conditions the desired product **36** was obtained in 52% yield. Next the reaction was attempted at -78 °C; again with 5 equivalents of Grignard being employed. In this case, the desired sulfoximine **36** was obtained in a much improved 55% yield. Changing the solvent to toluene caused a reduction in yield (48%) and the superior solvent was found to be THF (65%). Reducing the equivalents of organometallic to three and one equivalents served to reduce the yield (54% and 31% respectively) as did raising the reaction temperature to -20 or 0 °C (59% and 41% respectively). The trifluorethyl derived sulfonimidate **12** produced lower yields of sulfoximine that the ethyl derivative **11**.

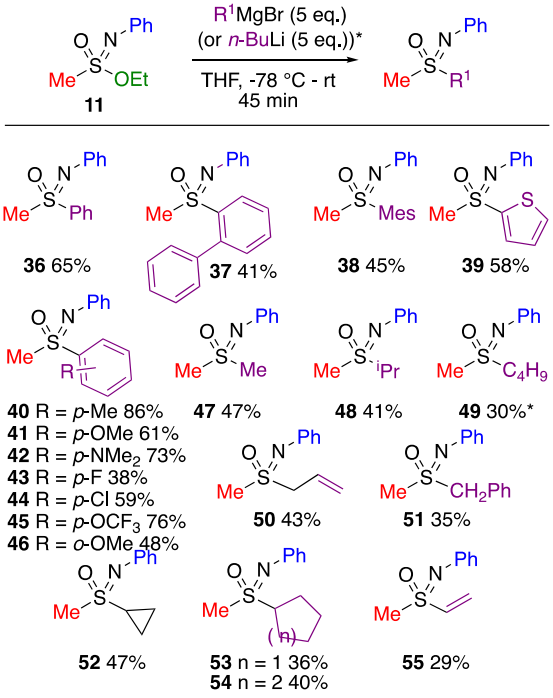


Figure 3. Synthesis of sulfoximines from the sulfonimidate **11**. Reactions were performed on a 0.1-0.2 mmol scale. Yields are for isolated products following chromatography.

With the optimized conditions in hand we set out to investigate the substrate scope of sulfoximine formation with respect to the organometallic component (Figure 3). Initially, aryl derived Grignard reagents were trialled (**36**-**46**), with product yields up to 86% being achieved. Increasing the steric bulk of the aryl Grignard from phenyl to biphenyl or mesityl led to an erosion in yield (41% and 45% respectively). Introduction of heteroaryl Grignards was also demonstrated to be possible with the 2-thienyl sulfoximine **39** being obtained in 58% yield. Monosubstituted aryl Grignard reagents were utilized with varying success (**40**-**46**), the best result was obtained when *para*-tolylmagnesium bromide was used (**40**, 86%). Employing linear or branched alkyl (and allyl) derived organometalic reagents allowed access to sulfoximines **47**-**50** in moderate to good yields (30-47% yield), the butyl sulfoximine **49** was accessed using *n*-butyl lithium in a moderate yield of 30%. Cycloalkyl moieties could also be incorporated; the *S*-cyclopropyl sulfoximine **52**, whose core structure can be mapped onto the drug molecule AZD 6738 (Figure 1), was generated in 47% yield. Vinyl sulfoximines have shown utility in the asymmetric synthesis of tetrahydrofurans,[12] oxabicycles[13] and pyrrolidines[14] and we were intrigued to investigate whether they could be produced using this methodology. Pleasingly, the vinyl sulfoximine **55** was isolated in 29%. We next investigated the formation of sulfoximines bearing alternative *N*- and *S*-substitution (Figure 4).

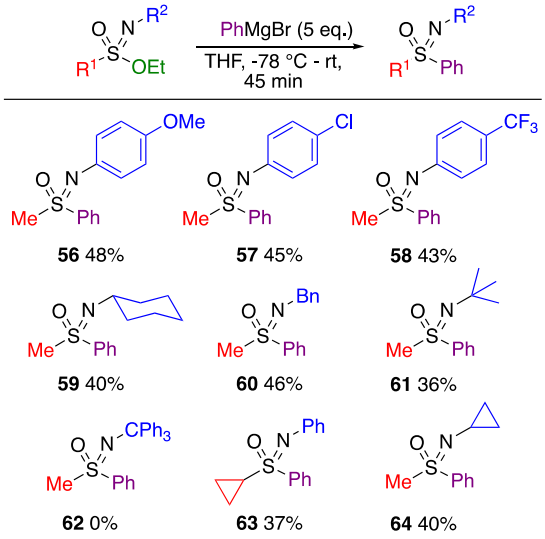


Figure 4. Further studies into the substrate scope for the synthesis of sulfoximines from sulfonimidates. Reactions were performed on a 0.1-0.2 mmol scale. Yields are for isolated products following chromatography.

Electron donating and withdrawing groups were tolerated comparably on *N*-aryl derivatives; the *para*-methoxy, -chloro and -trifluomethyl sulfoximines **56**-**58** were obtained in 43-48%. We next investigated substrates bearing *N*-alkyl substituents; *N*-cyclohexyl, -benzyl, -*tert*-butyl and -cyclopropyl sulfoximines **59**-**61** were formed in moderate yields (36-46%). A limit to the methodology was found with trityl sulfoximine **62**, which we were unable to form under the optimized conditions. Pleasingly however, both *S*- and *N*-cyclopropyl sulfoximines **63** and **64** could be obtained using this method, in 37% and 40% yield respectively.

In conclusion, a general method for the synthesis of sulfoximines has been developed that proceeds *via* C-S bond formation. The procedure utilizes the reaction of organometallic reagents with sulfonimidates, a class of compounds that have not been widely employed as precursors to sulfoximines. To compliment this strategy, the scope of sulfonimidate formation *via* the oxidation of sulfinamides has been expanded to include *S*-alkyl substrates for the first time.

ASSOCIATED CONTENT

Supporting Information

General synthetic procedures and characterization and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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