A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: Synthesis of Sulfonimidamides from Sulfenamides via an Alkoxy-amino-λ6-sulfanenitrile Intermediate

Authors: Edward L. Briggs, Arianna Tota, Marco Colella, Leonardo Degennaro, Renzo Luisi, and James Adam Bull

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201906001
Angew. Chem. 10.1002/ange.201906001

Link to VoR: http://dx.doi.org/10.1002/anie.201906001
http://dx.doi.org/10.1002/ange.201906001

WILEY-VCH

10.1002/anie.201906001

WILEY-VCH

RESEARCH ARTICLE

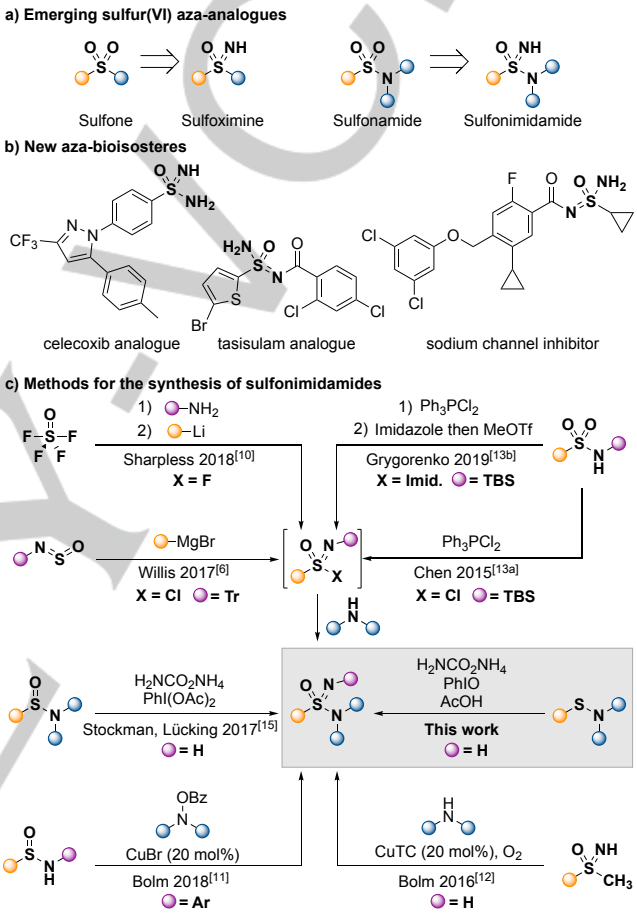
Synthesis of Sulfonimidamides from Sulfenamides via an Alkoxy-amino-λ^6-sulfanenitrile Intermediate

Edward L. Briggs,[a] Arianna Tota,[b] Marco Colella,[b] Leonardo Degennaro,[b] Renzo Luisi*[b] and James A. Bull*[a]

Abstract: Sulfonimidamides are intriguing new motifs for medicinal and agrochemistry, and provide attractive bioisosteres for sulfonamides. However, there remain few operationally simple methods for their preparation. Here, for the first time the synthesis of NH-sulfonimidamides is achieved directly from sulfenamides, themselves readily formed in 1 step from amines and disulfides. A highly chemoselective and one-pot NH and O transfer is developed, mediated by PhIO in *i*PrOH, using ammonium carbamate as the NH source, and in the presence of 1 equivalent of acetic acid. A wide range of functional groups are tolerated under the developed reaction conditions, including the functionalization of anti-depressants desipramine and fluoxetine. Additionally, the methodology is applied to the preparation of an aza-analogue of the drug probenecid, with further N-functionalization reactions exemplified on this scaffold. The reaction is shown to proceed via different and concurrent mechanistic pathways, including the formation of novel S≡N sulfanenitrile species as intermediates. Several alkoxy-amino-λ^6-sulfanenitriles are prepared with different alcohols, and shown to be alkylating agents to a range of nucleophiles. Detailed mechanistic studies demonstrate the *i*PrOH as one source of the sulfonimidamide oxygen atom, in addition to water and acetate.

Introduction

The adoption of unusual functional groups into medicinal and agrochemical research programs provides enhanced coverage of both chemical and intellectual property space.[1] Sulfoximines and sulfonimidamides, the mono-aza analogues of sulfones and sulfonamides respectively are receiving considerable attention in this context as bioisosteres in drug design (Scheme 1a).[2,3] High metabolic and chemical stability, along with hydrogen bond donor/acceptor capabilities can impart improved physicochemical properties to these aza-derivatives.[2] Sulfoximines have recently received extensive examination in clinical drug candidates from Bayer,[4] and AstraZeneca.[5] The sulfonimidamide group on the other hand has been less developed, but presents similar opportunities. Biologically active examples of sulfonimidamides include the aza-analogues of sulfonamides celecoxib[6] and tasisulam,[7] as well as a sodium channel inhibitor published by Genentech in a patent application (Scheme 1b).[8] This interest has prompted several recent synthetic advances (Scheme 1c).[9] Selected examples include Willis' use of N-sulfinyltritylamine as a linchpin for the addition of Grignard reagents and amines, via sulfonimidoyl chlorides.[6] Sharpless described the use of thionyl tetrafluoride (SOF_4) as a useful reagent for sulfur fluoride exchange (SuFEx) click chemistry, using sulfonimidoyl fluorides as precursors to sulfoximines, sulfonimidates and sulfonimidamides.[10] Bolm has reported copper catalyzed methods to form sulfonimidamides involving a cross coupling of



Scheme 1. Examples of bioactive sulfonimidamides, and strategies for the synthesis of sulfoximines and sulfonimidamides via NH and O transfer to sulfur functional groups.

[a] E. L. Briggs and Dr J. A. Bull
Department of Chemistry, Imperial College London, Molecular Sciences Research Hub, White City Campus, Wood Lane W12 0BZ, UK
E-mail: j.bull@imperial.ac.uk
Homepage: http://www3.imperial.ac.uk/people/j.bull
[b] A. Tota, M. Colella, Dr. L. Degennaro and Prof. Dr. R. Luisi
Department of Pharmacy-Drug Sciences, University of Bari "A. Moro"
Via E. Orabona 4, Bari 70125. Italy.
E-mail: renzo.luisi@uniba.it
Homepage:http://www.farmchim.uniba.it/chimica_organica/Luisi2.html

Supporting information for this article is given via a link at the end of the document.

10.1002/anie.201906001

sulfinamides[11] and the oxidation of methyl sulfoximines.[12] Sulfonamides have also been converted to sulfonimidamides with this approach being recently extended by Grygorenko to form imidazolium salts as precursors to sulfonimidamides and imidosulfuric diamides.[13]

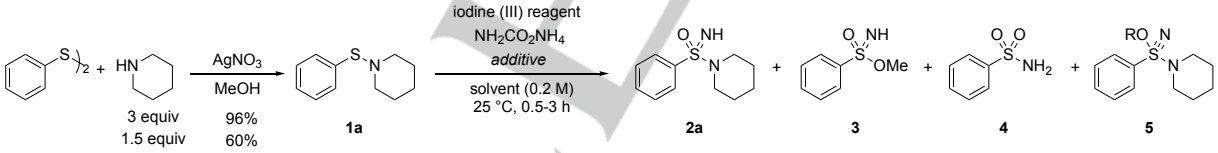
In 2016 we reported a facile metal-free protocol for the direct synthesis of NH-sulfoximines from sulfoxides in high yields and functional group compatibility.[14] The NH-transfer occurred with sources of ammonia, with ammonium carbamate preferred, in the presence of bisacetoxyiodobenzene as the oxidant. Our approach has been recently extended by Stockman and Lücking to form sulfonimidamides, using closely related conditions to effect NH-transfer to sulfinamides (Scheme 1c).[15] We, and others, recently reported related conditions for the conversion of sulfides to sulfoximines in one-pot through a highly chemoselective NH and O transfer.[16-18]

Here we report the development of a new strategy for the direct synthesis of NH-sulfonimidamides from sulfenamides as simple, readily available, and previously unexplored substrates. A highly selective one-pot NH and O transfer is achieved using operationally simple conditions. This provides a new and efficient disconnection of sulfonimidamides, allowing their preparation from functionalized amines and disulfides. Furthermore, we present detailed mechanistic studies on the reaction. Key intermediate alkoxy-amino-λ^6-sulfanenitriles have been isolated and characterised, providing insight to the reaction mechanism. The reactivity of these new λ^6-sulfanenitriles with nucleophiles is demonstrated. Overall, this strategy provides a short, 2-step synthetic sequence for the preparation of NH-sulfonimidamides that is applicable to late-stage diversification.

Results and Discussion

Bench-stable sulfenamides used in this study, were readily prepared starting from disulfides and a suitable amine.[19,20] As a model substrate for optimization, sulfenamide **1a** was prepared from Ph_2S_2 and piperidine in the presence of silver nitrate (Table 1), using a procedure modified from that developed by Davis.[21,22] We started investigations by applying our previously reported reaction conditions using $PhI(OAc)_2$ and ammonium carbamate.[14] Pleasingly, the expected sulfonimidamide **2a** was observed as the main product. Sulfonimidate **3** and sulfonamide **4** were also formed, with the loss of the piperidine moiety (Table 1, entry 1). The equivalents of oxidant and ammonium carbamate could be reduced to 2.5 and 2 respectively without affecting the reaction yield (entry 2), while further reduction of the equivalents of the oxidant resulted in incomplete conversion. Changing the solvent to *i*PrOH gave an improved yield of **2a** (entry 3). We noticed that excess acid, derived from the oxidant, was responsible for degradation of the sulfenamide and formation of side products. In fact, the use of a base such as NaOH as an additive (entry 4), resulted in a slightly improved yield of **2a**. In order to reduce the amount of acidic species, we investigated iodosylbenzene as the oxidant, which is known to dissolve in MeOH to form $PhI(OMe)_2$, without the formation of acid. Remarkably, the use of this reagent led to a lower yield of **2a** (entry 5) but a 47% yield of a new product, identified as an unprecedented alkoxy-amino-λ^6-sulfanenitrile (**5a**). Optimized conditions, leading to a 90% yield of sulfonimidamide **2a**, were achieved using *i*PrOH as the solvent, PhIO as the oxidant (2.5 equiv), and only 1 equiv of added acetic acid (entry 8).

Table 1. Selected results in the development and optimization of NH and O transfer to sulfenamides.



Entry	$NH_2CO_2NH_4$ (equiv)	$PhI(OAc)_2$ (equiv)	PhIO (equiv)	Additive (equiv)	Solvent	Yield[a]				
						2a	**3**	**4**	**5**	Total
1	4	3	-	-	MeOH	56	11	6	-	73
2	2	2.5	-	-	MeOH	56	11	3	-	70
3	2	2.5	-	-	*i*PrOH	60	6	10	-	76
4	2	2.5	-	NaOH (6)	MeOH	64	6	11	-	81
5	2	-	2.5	-	MeOH	11	2	3	47 (R = Me, **5a**)	63
6	2	-	2.5	AcOH (1)	MeOH	52	5	3	-	60
7	2	-	2.5	AcOH (5)	MeOH	51	11	8	-	70
8	**2**	**-**	**2.5**	**AcOH (1)**	***i*PrOH**	**90**	**2**	**1**	**-**	**93**
9	2	-	2.5	-	*i*PrOH	27	1	1	53 (R = *i*Pr, **5b**)	82

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard.

10.1002/anie.201906001

WILEY-VCH

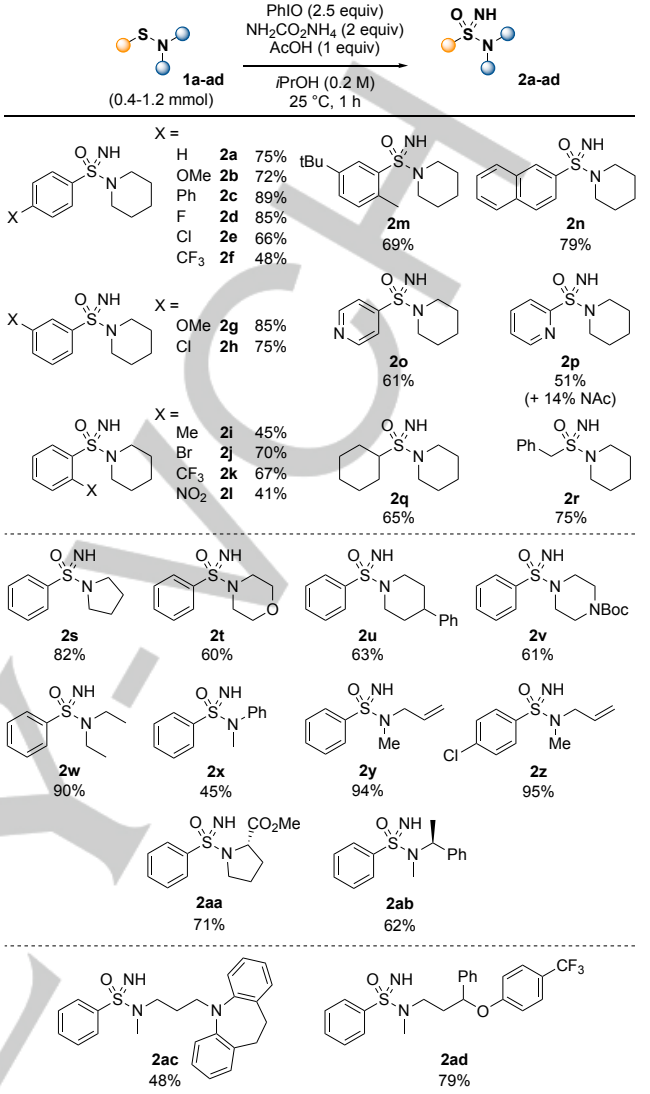
RESEARCH ARTICLE

The use of *i*PrOH reduced alternative unproductive pathways and afforded very high chemoselectivity for the heteroatom transfers. Increasing or decreasing the amount of acid gave unsatisfactory results. Interestingly, running the reaction under the optimized conditions but without the acid, produced the alkoxy-amino-λ^6-sulfanenitrile **5b** in a 53% yield, while **2a** was formed in only 27% yield (entry 9).

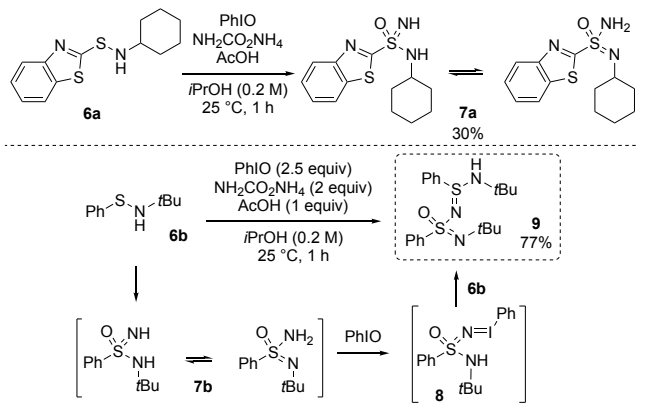
Using these optimized conditions, the scope of the reaction was assessed with different sulfenamides, varying substituents on both sides of the functional group (Scheme 2). It is worth noting the facile and rapid preparation of sulfenamides as sulfonimidamide precursors,[22] in comparison to sulfinamides for example, which often require extra steps and/or formation of sulfinylchlorides. First, piperidine-substituted sulfenamides **1a-1r** bearing several aromatics, heteroaromatics and alkyl substituents were evaluated. Sulfonimidamides **2a-2r** were obtained in yields ranging from 45% to 89%. Sulfonimidamide **2a** was isolated in 75% yield on a 0.5 mmol scale, and the reaction could be scaled to 9 mmol to provide 1.3 g of **2a** in 64% yield. Several substituted aromatics were compatible with the protocol, regardless of the position of the substituents (i.e. *ortho*-, *meta*- or *para*-) providing sulfonimidamides **2b-2l** (Scheme 2). Aromatic groups with varied electronic properties were tolerated, though the presence of electron-donating groups generally gave slightly higher yields when compared to aromatics bearing electron-withdrawing groups. Disubstituted phenyl and 2-naphtyl substituents furnished the corresponding NH-sulfonimidamides **2m** and **2n** respectively. Pyridine containing sulfenamides **1o** and **1p** substituted at the 2- and 4-positions were well tolerated (**2o** and **2p**), as were an alkyl (cyclohexyl, **2q**) and benzyl substituents (**2r**).

The variation of the amino moiety of the sulfenamide was then evaluated (Scheme 2). Cyclic amino substituents, including those bearing additional heteroatoms, furnished good to excellent yields of the corresponding NH-sulfonimidamides **2s-2v** (Scheme 2). Acyclic secondary amines, bearing diethyl (**2w**), methylphenyl (**2x**) and allyl substituents (**2y** and **2z**) were similarly successful. Using sulfenamides **1aa** and **1ab** prepared from chiral amines provided NH-sulfonimidamides **2aa** and **2ab** in good yields as a 1:1 mixture of diastereoisomers, with complete retention of the enantiomeric excess of the chiral starting amines.[22,23] Sulfenamides **1ac** and **1ad** derived from anti-depressant drugs desipramine and fluoxetine yielded sulfonimidamide analogues **2ac** and **2ad** (*dr* 1:1) in 48% and 79% yields respectively, illustrating the potential of the method for late stage functionalization.

Secondary sulfenamide substrates containing an NH were then evaluated, affording interesting results. Benzothiazole containing sulfenamide **6a** gave sulfonimidamide **7a** in 30% isolated yield, along with the corresponding sulfinamide as the major side product. In comparison, *t*-butylphenylsulfenamide **6b** unexpectedly gave product **9**, incorporating 2 molecules of **6b** in high yield. This was presumably formed through activation of the expected sulfonimidamide **7b** with excess oxidant, leading to iminoiodinane intermediate **8** and subsequent imination of **6b** (Scheme 3).[24] Application of these conditions to phenyl methyl sulfide yielded the corresponding NH-sulfoximine in 83% isolated yield,[22] providing an alternative for the formation of sulfoximines from sulfides.[16,17]



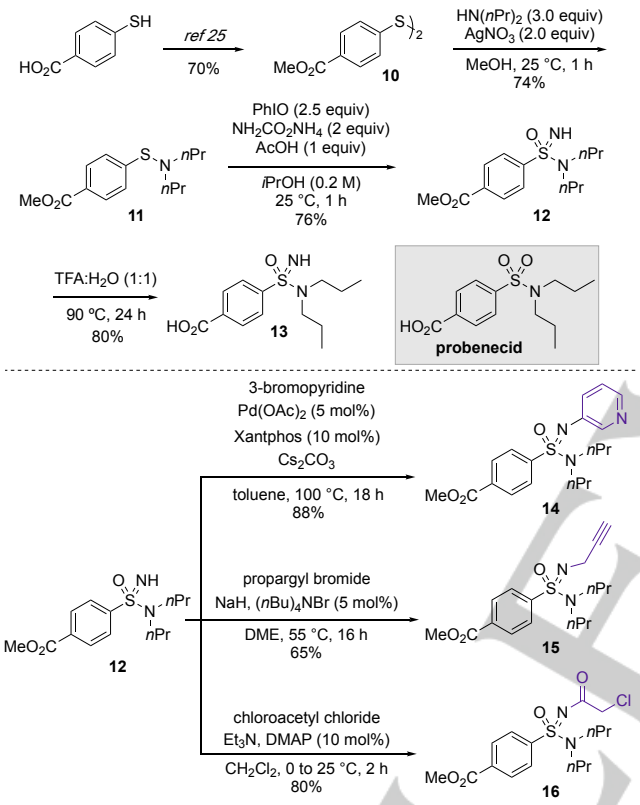
Scheme 2. Reaction scope varying the sulfenamide substrate to form NH sulfonimidamides by NH and O transfer.



Scheme 3. Reactivity of secondary sulfenamides **6** under NH and O transfer conditions.

10.1002/anie.201906001

To further demonstrate the utility of this method for the preparation of drug-like compounds, a sulfonimidamide analogue of probenecid was prepared (Scheme 4). Probenecid is a sulfonamide containing drug on the market for the treatment of hyperuricemia. Synthesis of the aza-analogue was achieved in 3 steps, in an overall yield of 45% from known disulfide **10**.[25] Disulfide **10** was readily converted to sulfenamide **11** using silver nitrate and dipropylamine. Applying the developed conditions for NH and O transfer furnished sulfonimidamide **12** in 76% yield. Finally, hydrolysis of the ester using TFA/H_2O at 90 °C gave the aza-analogue of the drug compound **13** and demonstrated stability of the sulfonimidamide functional group to acid.



Scheme 4. Synthesis of probenecid analogue **13** and NH functionalization to enhance coverage of chemical space.

To display the potential of the sulfonimidamide group to explore broader chemical space than their oxo-analogues, N-functionalization of intermediate **12** was undertaken (Scheme 4).[26] Pd catalyzed cross-coupling introduced a pyridyl group, installing further medicinally relevant functionality.[26a] Alkylation with propargyl bromide and acylation with chloroacetyl chloride gave **15** and **16** respectively, introducing functionality commonly employed in chemical biology, as a click handle or in covalent probes respectively.

The isolation of the unusual alkoxy-amino-λ^6-sulfanenitriles **5a** and **5b** (Table 1) presented intriguing structures that were likely to be immediate precursors to the sulfonimidamide in the mechanism. There are very few reports of related S≡N containing compounds. In 1989, Yoshimura[27] reported an example of an alkoxy-λ^6-sulfanenitrile **17** (Figure 1). This was a powerful alkylating agent, readily converting to the corresponding sulfoximine by transfer of the R group.[28] In 2017, Reboul described alkoxy-λ^6-sulfanenitrile **18** in the mechanistic investigation on the NH, and O transfer to sulfides to form sulfoximines.[17a] Compounds **5a** and **5b** isolated here represent a new class of λ^6-sulfanenitrile, and have been fully characterized (IR, ^{1}H and ^{13}C NMR and HRMS) along with small quantities of the corresponding sulfonimidamide. The calculated S≡N IR stretch (DFT) was consistent with that observed for **5b**, and for **17**.[22] In situ IR experiments in the absence of acid also indicated formation of an intermediate ascribed as **5b** (1387 cm^{-1}).[22] Compounds **5a** and **5b** readily converted to the sulfonimidamide on silica, and were not observed in the presence of added AcOH. In situ ^{1}H NMR studies corroborated that the breakdown of the alkoxy-amino-λ^6-sulfanenitrile to the sulfonimidamide is rapid in the presence of acid, or slow in the absence of acid in MeOD solution.[22]

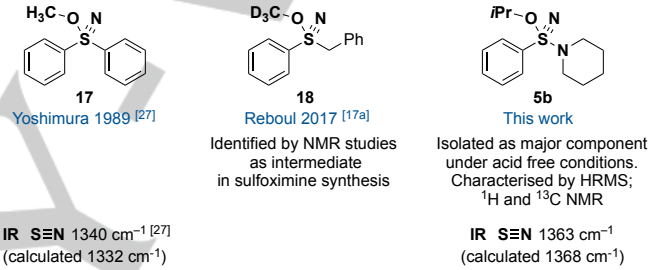
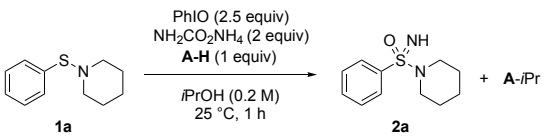


Figure 1. Prior reports of alkoxy-λ^6-sulfanenitriles, and comparison of key data obtained for alkoxy-amino-λ^6-sulfanenitrile **5b**.

Studies were undertaken to elucidate the mechanism of conversion of alkoxy-amino-λ^6-sulfanenitriles **5b** to sulfonimidamide **2a**. Firstly, other acids were included in the standard reaction of sulfenamide **1a** (Table 2). When benzoic acid was used in place of AcOH a similarly high yield of **2a** was obtained (entries 1 & 2). Pleasingly, the less volatile isopropyl benzoate was detected in a 48% yield. This was presumed to be protonation of the S≡N group promoting alkylation of either the conjugate base or another nucleophile (e.g. solvent). In the presence of *p*TsOH a reduced yield of **2a** was achieved but with the same amount of *p*TsO*i*Pr formed, indicating all of the formed **2a** was derived from attack of the sulfonate anion at the isopropyl group of **5b** (entry 3).

10.1002/anie.201906001

Table 2. Role of different acids in formation of **2a** and in breakdown of intermediate alkoxy-amino-λ^6-sulfanenitrile.

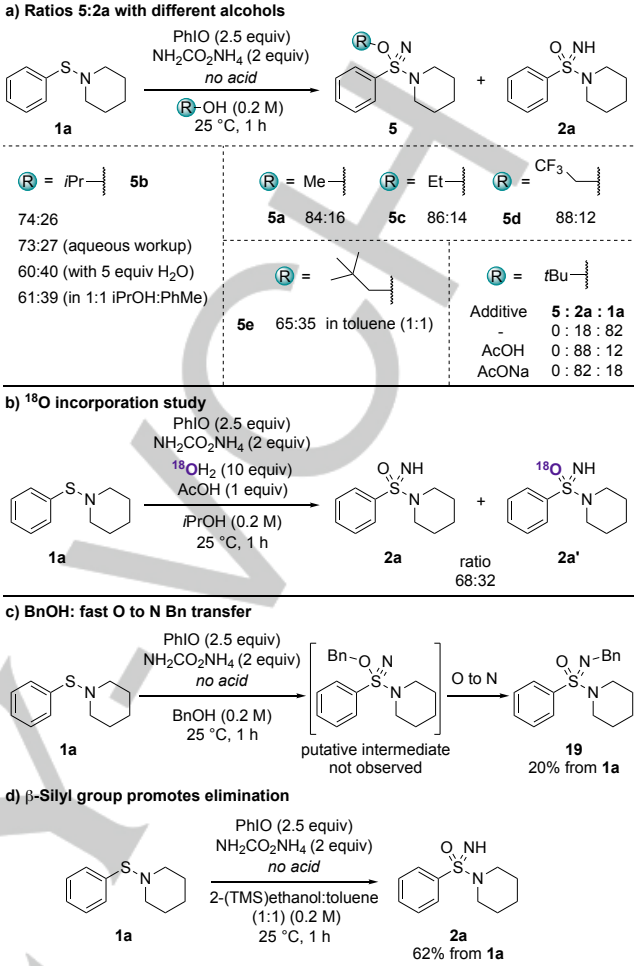


Entry	A-H	Yield[a]	
		2a	**A–*i*Pr**
1	AcOH	90	-[b]
2	PhCOOH	89	48
3	*p*TsOH	30[c]	29

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard. [b] Observed during in-situ ^{1}H NMR experiments. See SI for further details. [c] Remaining starting material decomposed.

Next, reactions were performed in the absence of added acetic acid to allow examination of the stability of the λ^6-sulfanenitrile species **5** (Scheme 5a). Using *i*PrOH as the reaction solvent gave a 74:26 ratio of **5b**:**2a** on evaporation of the reaction mixture as determined by ^{1}H NMR. The same result was obtained with an aqueous work up indicating the stability of **5b** to water. Doping the reaction with water (5 equiv) led to increased conversion to **2a**, suggesting an alternative possible pathway that incorporated H_2O directly. To further confirm this, $^{18}OH_2$ was added to the reaction (with acetic acid), and mass spectrometry of the obtained sulfonimidamide product indicated incorporation of ^{18}O in the in a roughly 1:2 ratio to the ^{16}O isotope (Scheme 5b).

Different alcohols were employed to form derivatives of the alkoxy-amino-λ^6-sulfanenitrile species **5**, examining the extent of conversion to the sulfonimidamide under the reaction conditions (Scheme 5a). In each case, the corresponding λ^6-sulfanenitrile was observed. Various primary alcohols gave increased amounts of **5**. To enable a broader range of solid alcohols, a mixture of alcohol in toluene was tested; as a reference *i*PrOH gave a 60:40 ratio of **5b**:**2a**. Neopentyl alcohol (in toluene), gave similar results to *i*PrOH. As a poor electrophile for SN1 and SN2 reactions, this is consistent with an alternative H_2O mediated pathway being operative to form **2a** in these examples. Using *t*BuOH was unsuccessful in forming the corresponding λ^6-sulfanenitrile, instead returning mainly **1a** and a small amount of **2a**. It is notable that PhIO has poor solubility in *t*BuOH, however, when one equiv. of either AcOH or AcONa were used in the reaction a good conversion to **2a** was observed, suggesting a crucial role of the acetate beyond just solubility. When benzyl alcohol was used as the reaction solvent, the λ^6-sulfanenitrile was not observed, with **2a** as the major product. Interestingly, rearrangement product **19** was also isolated, presumably by intermolecular benzylation due to the λ^6-sulfanenitrile being a highly reactive benzylating agent. Finally, 2-trimethylsilylethanol was investigated expecting to further destabilize the intermediate to allow conversion to the sulfonimidamide through silyl promoted elimination. This was indeed the case, providing an increased ratio of sulfonimidamide **2a** to λ^6-sulfanenitrile (15:85) which allowed for isolation of **2a** under acid free conditions in a 62% yield.



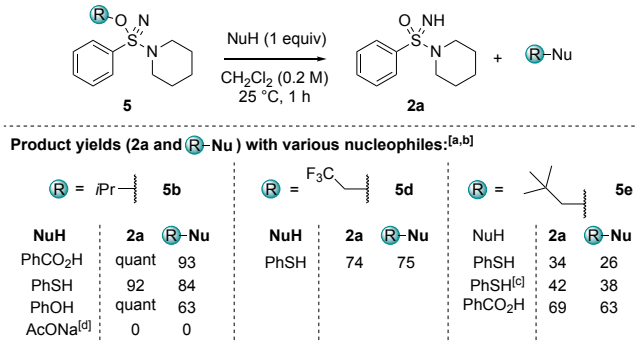
Scheme 5. Formation of various alkoxy-amino-λ^6-sulfanenitriles **5**.

The reactivity of alkoxy-amino-λ^6-sulfanenitriles **5b**, **5d** and **5e** with acidic nucleophiles was then investigated (Scheme 6). Treating λ^6-sulfanenitrile **5b** with benzoic acid in anhydrous CH_2Cl_2 gave high yields of **2a** and the corresponding alkylated product. Thiophenol and phenol were also suitable nucleophiles. Intriguingly, AcONa did not convert any of the λ^6-sulfanenitrile to **2a** showing the need for a prior protonation before alkylation can take place. The 2,2,2-trifluoroethyl group of **5d** was transferred to thiophenol in 75% yield, with overall activation of trifluoroethanol. Furthermore, stirring **5e** containing the highly sterically hindered neopentyl group with thiophenol led to alkylation in low yield with a slight improvement in yield when the reaction time was extended to 3 days. More strongly acidic conditions using benzoic acid led to a good yield (63%) of the neopentyl ester product.

10.1002/anie.201906001

WILEY-VCH

RESEARCH ARTICLE

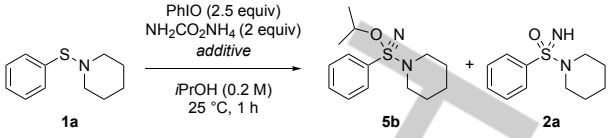


Scheme 6. Formation of various alkoxy-amino-λ^6-sulfanenitriles **5** and their reactivity with different nucleophiles. [a] Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard. [b] The amount of **2a** corresponds to the amount of **2a** formed in the reaction after subtraction of that already present in the mixture deriving from the synthesis of **5** (37% with **5b**, 13% **5d** and 35% **5e**). [c] Reaction time extended to 72 h. [d] *i*PrOH used as a co-solvent to solubilize AcONa (1:1).

It is apparent from intermediate alkoxy-amino-λ^6-sulfanenitriles that the O atom originates from the solvent through this pathway. The protonated alkoxy-amino-λ^6-sulfanenitriles are powerful electrophiles. These results are suggestive of a combination of SN1 and SN2 pathways being operative, and that the conjugate base is likely to be the nucleophile. The use of isopropanol provides a cleaner overall reaction than other solvents, which may be due to the balance it offers of higher nucleophilicity (*cf* *t*BuOH), as well as effective substitution pathways.

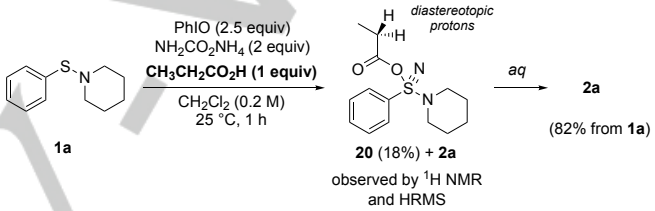
Finally, we considered potential differences in the reaction mechanism in the presence of the acetic acid. The influence of sodium acetate on the reaction in *t*BuOH (Scheme 5), and the inability of NaOAc to break down the sulfanenitrile (Scheme 6), suggested an additional role for acetate in the reaction mechanism. When sodium acetate was used as an additive under the full reaction conditions, in place of acetic acid, **2a** was formed in a 73% yield (Table 3, entry 1). When using tetrabutylammonium acetate essentially the same product distribution was seen indicating that there is no effect from the sodium counterion on the λ^6-sulfanenitrile (entry 2). Importantly, the alkoxy-amino-λ^6-sulfanenitrile **5b** was also observed in both cases. This suggested a third pathway where an intermediate acetoxy-amino-λ^6-sulfanenitrile is formed, such a species could break down rapidly via attack of the alcohol solvent to form **2a**. Interestingly, sodium benzoate afforded an increased amount of the alkoxy-amino-λ^6-sulfanenitrile **5b** perhaps due to its reduced nucleophilicity (entry 3). Performing the standard reaction using AcOH, but in CH_2Cl_2 rather than *i*PrOH gave intermediate products that could be putatively assigned as an acetoxy-amino-λ^6-sulfanenitrile by ^{1}H NMR of the crude reaction mixture following evaporation. Exposure of the sample to water led to immediate breakdown to sulfonimidamide **2a**. Using propionic acid in place of AcOH gave further support for this unstable intermediate, with the observation of diastereotopic methylene protons derived from the propionate in the λ^6-sulfanenitrile, which was also characterized by high resolution mass spectrometry (Scheme 7).[22]

Table 3. Product distribution when using carboxylate salts.



Entry	Additive	Yield[a]		
		5b	**2a**	**1a**
1	AcONa	9	73	10
2	$AcONBu_4$	7	74	13
3	$PhCO_2Na$	55	36	12

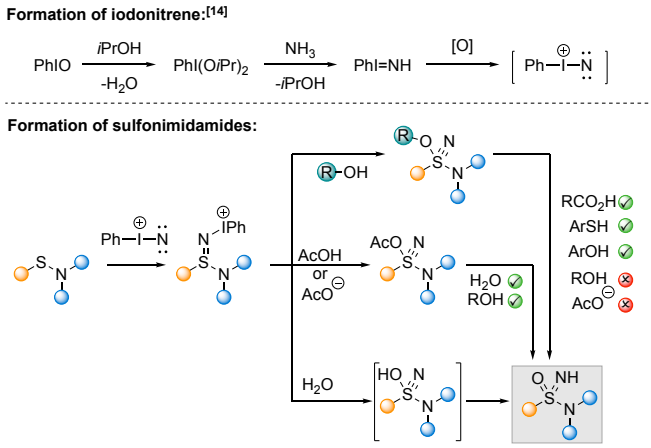
[a] Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard.



Scheme 7. Identification of an acyl-amino-λ^6-sulfanenitrile as a putative intermediate.

Therefore, mechanistically we propose the following, as shown in Scheme 8. Initial solubilization of PhIO occurs through condensation with *i*PrOH. A highly reactive iodonitrene species is then formed from the oxidant and ammonia. We have previously detected this short-lived intermediate via HRMS studies with ^{15}N labelled ammonia.[14] The iodonitrene rapidly reacts with the sulfenamide to form a sulfinamidine salt. The elimination of iodobenzene from this species to form the S≡N triple bond may occur before or at the same time as attack of a suitable nucleophile. Under the reaction conditions, 3 possible nucleophiles can attack at the sulfur centre. Addition of the abundant alcohol solvent forms the alkoxy-amino-λ^6-sulfanenitrile. This is relatively stable under neutral conditions, but becomes a powerful alkylating agent in mild acidic conditions. Alternatively, attack of acetate provides an unstable intermediate that readily converts to the sulfonimidamide through the action of solvent. Finally, the addition of water, present in the solvent or generated from the solubilization of iodosylbenzene can lead directly to the sulfonimidamide. It is notable that each possible pathway leads to the same product, conferring the remarkably high chemoselectivity to the reaction.

10.1002/anie.201906001



Scheme 8. Proposed mechanism of sulfonimidamide formation.

Conclusion

In summary, we have developed an efficient method for the preparation of NH-sulfonimidamides from sulfenamides. A highly selective one-pot NH and O transfer is achieved, using a simple ammonia source and a hypervalent iodine reagent. The use of iodosylbenzene allows for control over the acidity of the reaction, with one equivalent of acetic acid optimal for formation of the desired sulfonimidamide. In the absence of added acid, an unprecedented alkoxy-amino-λ^6-sulfanenitrile is isolated as a reaction intermediate. The isolation and characterization of several examples of this novel species provides insight into the reaction mechanism, and identifies the solvent as one source of the oxygen atom in the product. These newly formed alkoxy-amino-λ^6-sulfanenitriles act as alkylating agents to a range of acidic nucleophiles. Other pathways through the addition of water or acetate are also operative. The sulfenamide to sulfonimidamide transformation is tolerant of a range of functional groups, displaying a wide substrate scope, including the functionalization of anti-depressants desipramine and fluoxetine. The method was used in the synthesis of an aza-analogue of the sulfonamide drug probenecid, as well as displaying possible useful N-functionalization reactions on this scaffold, demonstrating the utility of the methodology for medicinal chemistry.

Acknowledgements

We gratefully acknowledge The Royal Society [University Research Fellowship, UF140161 (to J. A. B.) and URF appointed grant RG150444, and URF enhancement grant, RGF\EA\180031], and EPSRC [CAF to J.A.B. (EP/J001538/1), Impact Acceleration Account (EP/K503733/1), DTA Studentship (to E.L.B.)]. This research was supported by the project MISE, Horizon 2020 – PON 2014/2020 FARMIDIAB "code 338", the University of Bari.

Keywords: hypervalent iodine • reactive intermediates • sulfur • sulfonimidamides • synthetic methods

[1] a) F. W. Goldberg, J. G. Kettle, T. Kogej, M. W. D. Perry, N. P. Tomkinson, *Drug Discov. Today* **2015**, *20*, 11; b) C. W. Murray, D. C. Rees, *Angew. Chem. Int. Ed.* **2016**, *55*, 488; *Angew. Chem.* **2016**, *128*, 498; c) J. A. Bull, R. A. Croft, O. A. Davis, R. Doran, K. F. Morgan, *Chem. Rev.* **2016**, *116*, 12150; Also see: d) D. C. Blakemore, L. Castro, I. Churcher, D. C. Rees, A. W. Thomas, D. M. Wilson, A. Wood, *Nat. Chem.* **2018**, *10*, 383; e) A. Nadin, C. Hattotuwagama, I. Churcher, *Angew. Chem. Int. Ed.* **2012**, *51*, 1114; *Angew. Chem.* **2012**, *124*, 1140.

[2] a) C. Gnamm, A. Jeanguenat, A. C. Dutton, C. Grimm, D. P. Kloer, A. J. Crossthwaite, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3800; b) P. K. Chinthakindi, T. Naicker, N. Thota, T. Govender, H. G. Kruger, P. I. Arvidsson, *Angew. Chem. Int. Ed.* **2017**, *56*, 4100; *Angew. Chem.* **2017**, *129*, 4160; c) U. Lücking, *Angew. Chem. Int. Ed.* **2013**, *52*, 9399; *Angew. Chem.* **2013**, *125*, 9570; d) M. Frings, C. Bolm, A. Blum, C. Gnamm, *Eur. J. Med. Chem.* **2017**, *126*, 225; e) F. Sehgelmeble, J. Janson, C. Ray, S. Rosqvist, S. Gustavsson, L. I. Nilsson, A. Minidis, J. Holenz, D. Rotticci, J. Lundkvist, et al., *ChemMedChem* **2012**, *7*, 396; f) S. R. Borhade, R. Svensson, P. Brandt, P. Artursson, P. I. Arvidsson, A. Sandström, *ChemMedChem* **2015**, *10*, 455; g) J. A. Bull, L. Degennaro, R. Luisi, *Synlett* **2017**, *28*, 2525; h) U. Lücking, *Org. Chem. Front.* **2019**, *6*, 1319.

[3] For sulfonimidamides as coordinating groups and ligands, see: a) J. Buendia, G. Grelier, B. Darses, A. G. Jarvis, F. Taran, P. Dauban, *Angew. Chem. Int. Ed.* **2016**, *55*, 7530; *Angew. Chem.* **2016**, *128*, 7656; b) J. Buendia, B. Darses, P. Dauban, *Angew. Chem. Int. Ed.* **2015**, *54*, 5697; *Angew. Chem.* **2015**, 127, 5789; c) M. Steurer, C. Bolm, *J. Org. Chem.* **2010**, *75*, 3301; d) C. Worch, C. Bolm, *Synlett* **2009**, *2009*, 2425.

[4] a) U. Lücking, R. Jautelat, M. Krüger, T. Brumby, P. Lienau, M. Schäfer, H. Briem, J. Schulze, A. Hillisch, A. Reichel, et al., *ChemMedChem* **2013**, *8*, 1067; b) U. Lücking, A. Scholz, P. Lienau, G. Siemeister, D. Kosemund, R. Bohlmann, H. Briem, I. Terebesi, K. Meyer, K. Prelle, et al., *ChemMedChem* **2017**, *12*, 1776.

[5] a) K. M. Foote, J. W. M. Nissink, T. McGuire, P. Turner, S. Guichard, J. W. T. Yates, A. Lau, K. Blades, D. Heathcote, R. Odedra, et al., *J. Med. Chem.* **2018**, *61*, 9889; b) F. P. Vendetti, A. Lau, S. Schamus, T. P. Conrads, M. J. O'Connor, C. J. Bakkenist, *Oncotarget* **2015**, *6*, 44289.

[6] T. Q. Davies, A. Hall, M. C. Willis, *Angew. Chem. Int. Ed.* **2017**, *56*, 14937; *Angew. Chem.* **2017**, *129*, 15133.

[7] A. D. Steinkamp, L. Schmitt, X. Chen, K. Fietkau, R. Heise, J. M. Baron, C. Bolm, *Skin Pharmacol. Physiol.* **2017**, *29*, 281.

[8] S. Chowdhury, C. M. Dehnhardt, T. Focken, M. E. Grimwood, I. W. Hemeon, S. McKerrall, D. Sutherlin (Genentech, Inc.), WO 2017172802, **2017**.

[9] For a review: G. C. Nandi, P. I. Arvidsson, *Adv. Synth. Catal.* **2018**, *360*, 2976.

[10] B. Gao, S. Li, P. Wu, J. E. Moses, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2018**, *57*, 1939; *Angew. Chem.* **2018**; *130*, 1957.

[11] H. Yu, Z. Li, C. Bolm, *Angew. Chem. Int. Ed.* **2018**, *57*, 15602; *Angew. Chem.* **2018**; *130*, 15828.

[12] J. Wen, H. Cheng, S. Dong, C. Bolm, *Chem. Eur. J.* **2016**, *22*, 5547.

[13] a) P. K. Chinthakindi, A. Benediktsdottir, A. Ibrahim, A. Wared, C.-J. Aurell, A. Pettersen, E. Zamaratski, P. I. Arvidsson, Y. Chen, A. Sandström, *Eur. J. Org. Chem.* **2019**, *2019*, 1045. b) S. V. Zasukha, V. M. Timoshenko, A. A. Tolmachev, V. O. Pivnytska, O. Gavrylenko, S. Zhersh, Y. Shermolovich, O. O. Grygorenko, *Chem. Eur. J.* **2019**, *25*, 6928.

[14] M. Zenzola, R. Doran, L. Degennaro, R. Luisi, J. A. Bull, *Angew. Chem. Int. Ed.* **2016**, *55*, 7203; *Angew. Chem.* **2016**, *128*, 7319.

[15] F. Izzo, M. Schäfer, R. Stockman, U. Lücking, *Chem. Eur. J.* **2017**, *23*, 15189.

[16] A. Tota, M. Zenzola, S. J. Chawner, S. St John-Campbell, C. Carlucci, G. Romanazzi, L. Degennaro, J. A. Bull, R. Luisi, *Chem. Commun.* **2017**, *53*, 348.

[17] For related reports at a similar time, see: a) J.-F. Lohier, T. Glachet, H. Marzag, A.-C. Gaumont, V. Reboul, *Chem. Commun.* **2017**, *53*, 2064; b) Y. Xie, B. Zhou, S. Zhou, S. Zhou, W. Wei, J. Liu, Y. Zhan, D. Cheng, M. Chen, Y. Li, et al., *ChemistrySelect* **2017**, *2*, 1620; Also see: c) S.

Chaabouni, J.-F. Lohier, A.-L. Barthelemy, T. Glachet, E. Anselmi, G. Dagousset, P. Diter, B. Pégot, E. Magnier, V. Reboul, *Chem. Eur. J.* **2018**, *24*, 17006.

[18] a) For formation of sulfonimidates from thiols: A. Tota, S. St John-Campbell, E. L. Briggs, G. O. Estévez, M. Afonso, L. Degennaro, R. Luisi, J. A. Bull, *Org. Lett.* **2018**, *20*, 2599; b) For synthesis of sulfoximine carbamates using Rh-catalysis, see: M. Zenzola, R. Doran, R. Luisi, J. A. Bull, *J. Org. Chem.* **2015**, *80*, 6391.

[19] L. Craine, M. Raban, *Chem. Rev.* **1989**, *89*, 689.

[20] For recent reviews including the synthesis of sulfenamides, see: a) F. Alsadat, H. Nasab, Z. Fekri, A. Monfared, *RSC Adv.* **2018**, *8*, 18456; b) O. M. Mulina, A. I. Ilovaisky, A. O. Terent'ev, *Eur. J. Org. Chem.* **2018**, *2018*, 4648.

[21] F. A. Davis, A. J. Friedman, E. W. Kluger, E. B. Skibo, E. R. Fretz, A. P. Milicia, W. C. LeMasters, M. D. Bentley, J. A. Lacadie, I. B. Douglass, *J. Org. Chem.* **1977**, *42*, 967.

[22] See SI for further details.

[23] Typically the sulfonimidamides were purified on neutral alumina, whereas compound **2aa** was purified on silica. One diastereoisomer of **2aa** converted preferentially on neutral alumina during purification to give a cyclic N-acyl sulfonimidamide, which was isolated in 74% yield from the reactive diastereoisomer. Both diastereoisomers could be slowly converted to the same cyclized product on stirring with alumina, due to epimerisation. See reference 13a and also SI for further details.

[24] For an example of $NsNH_2$ transfer to sulfoxides in the presence of $PhI(OAc)_2$, see: G. Y. Cho, C. Bolm, *Tetrahedron Lett.* **2005**, *46*, 8007.

[25] E. Carbonnel, T. Besset, T. Poisson, D. Labar, X. Pannecoucke, P. Jubault, *Chem. Commun.* **2017**, *53*, 5706.

[26] NH-sulfonimidamide products can be functionalised at nitrogen, see: (*a*) F. Izzo, M. Schäfer, P. Lienau, U. Ganzer, R. A. Stockman, U. Lücking, *Chem. Eur. J.* **2018**, *24*, 9295. See SI for further examples of N-arylation of **2b**, **2h**, **2s** and **2z**; (*b*) G. C. Nandi, S. R. Kota, T. Govender, H. G. Kruger, P. I. Arvidsson, *Tetrahedron* **2014**, *70*, 5428.

[27] T. Yoshimura, E. Tsukurimichi, H. Kita, H. Fujii, C. Shimasaki, *Tetrahedron Lett.* **1989**, *30*, 6339.

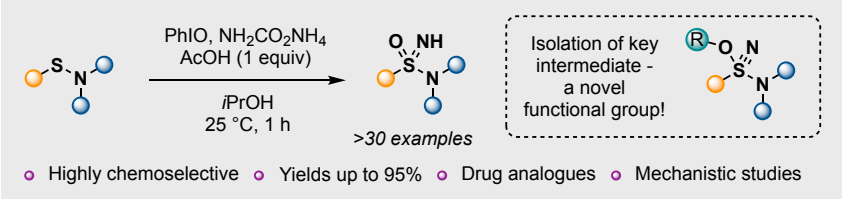
[28] W. Hao, T. Fujii, T. Dong, Y. Wakai, T. Yoshimura, *Heteroat. Chem.* **2004**, *15*, 193.

10.1002/anie.201906001

WILEY-VCH

Layout 2:

RESEARCH ARTICLE



NH and O transfer: Convenient reagents for NH and O transfer allow the direct preparation of NH sulfonimidamides from sulfenamides. A wide range of diversely functionalized sulfonimidamides are prepared in high yields using mild reagents in just two steps from commercial starting material. Novel alkoxy-amino-λ^6-sulfanenitriles are isolated and their reactivity demonstrated for the first time.

E. L. Briggs, A. Tota, M. Colella, L. Degennaro, R. Luisi and J. A. Bull**

Page No. – Page No.

Synthesis of Sulfonimidamides from Sulfenamides via an Alkoxy-amino-λ^6-sulfanenitrile Intermediate