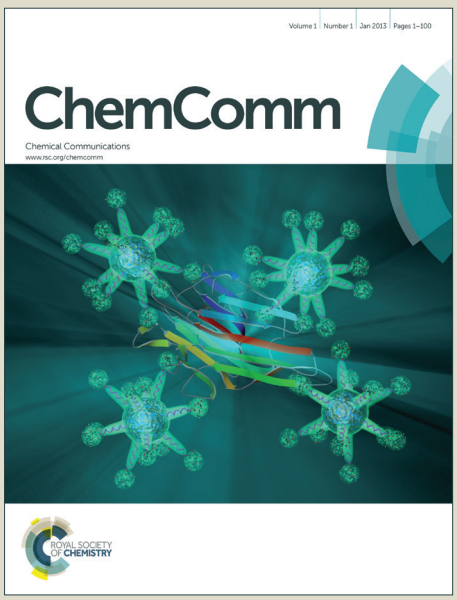
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Isolation of stable non cyclic 1,2-Disulfoxides. Revisiting the thermolysis of *S*-aryl sulfinimines

José A. Souto,*[a,b] Willian Lewis [§a] and Robert A. Stockman*[a]

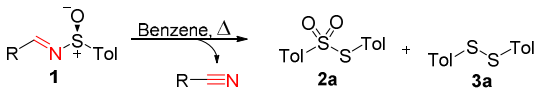
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

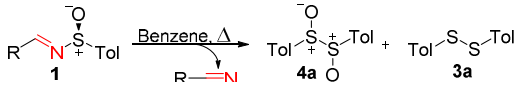
The thermolysis of *S*-aryl sulfinimines is shown to generate 1,2-disulfoxides and disulfides via initial Cope elimination, dimerisation of the produced sulfenic acid to a thiosulfinate, and subsequent disproportionation of the thiosulfinate.

The nitrogen-carbon double bond (imine group) is a versatile moiety in synthetic organic chemistry, which is able to act as an electrophile, nucleophile or in concerted cycloadditions. Chiral sulfinimines have come to the fore as one of the most useful imine derivatives. Introduced over 20 years ago,[1] they have found extensive use both in academia and industry. Their practicality is conferred by the electron-withdrawing nature of the chiral sulfinyl group that is also able to dictate the stereochemical outcome of transformations, such as the asymmetric synthesis of α-branched amines, allylic, homoallylic and propargylic amines, tertiary carbinamates, highly substituted aminoacids, 1,2 aminoalcohols, 1,2 and 1,3 diamines, and aziridines among others.[2] Herein we report a surprising thermal degradation of sulfinimines, which may have implications for those working with certain types of sulfinimine, for example in pharmaceutical manufacture.

a. Previously:



b. This work:

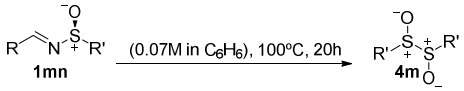


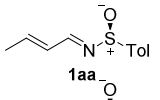
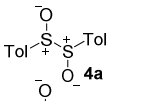
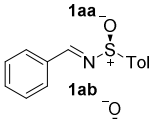
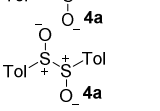
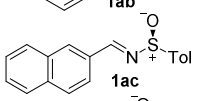
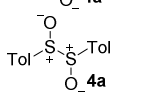
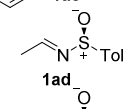
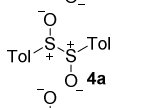
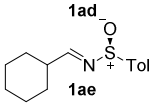
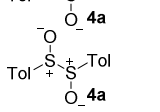
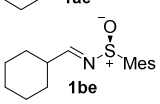
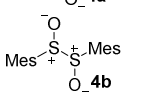
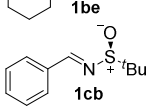
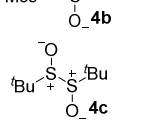
Scheme 1. Thermal degradation of sulfinimines.

As part of a study to extend the scope of reactivity of sulfinimine derivatives, and due to our on-going interest in the synthesis of heterocycles,[3] we started an investigation into the hetero Diels-Alder reaction[4] between crotonsulfinimine **1aa** and an equimolar amount of ethyl vinyl ether as dienophile. Our attempts to perform the desired transformation were unsuccessful; however, two unexpected products were isolated that were identified as the disulfoxide **4a** and the corresponding disulfide **3a**. The reaction in the absence of the dienophile did not afford any change in the reaction overcome previously detected. Due to the previously mentioned importance of sulfinimine derivatives in industrial processes, and routine organic synthesis, we decided to study this transformation further, to assess the generality of this reaction.

Initially, we screened different solvents and conditions observing clear differences in the ratio of the two products depending on the experimental procedure followed. In general, benzene proofed to be the best solvent and the reaction showed a clear dependence on the concentration.[5] We next screened to determine whether modification of the starting material either by replacement of the croton unit or the *p*-toluensulfonyl moeity in the nitrogen would

Table 1. Thermal degradation of different sulfinimines.



Entry	Sulfinimine	Disulfoxide	Yield [%][a]
1	 1aa	 4a	50
2	 1ab	 4a	63
3	 1ac	 4a	36
4	 1ad	 4a	66
5	 1ae	 4a	51
6	 1be	 4b	45[b]
7	 1cb	 4c	0

[a] Isolated yield after purification. Scale, 0.5 mmol. [b] 70ºC.

[a] *School of Chemistry, University of Nottingham, Nottingham, NG7 2RD, UK. Fax: 0044 115 951356; E-mail: robert.stockman@nottingham.ac.uk*

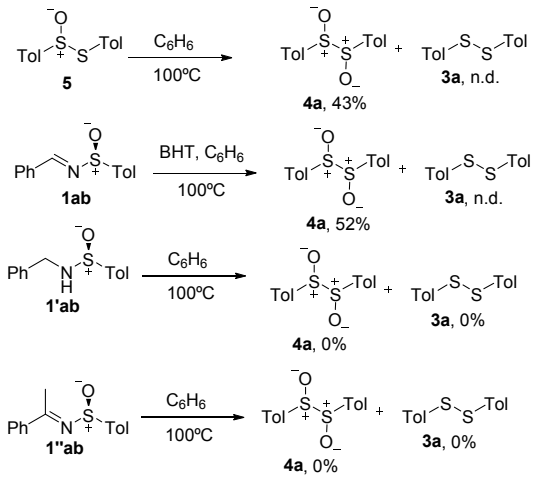
[b] *Departamento de Química Orgánica, Universidade de Vigo, Vigo, 36315 Spain; E-mail: souto@uvigo.es*

† Electronic Supplementary Information (ESI) available: See DOI: 10.1039/b000000x/

§ Author to whom correspondance about X-ray structure determination should be directed. Email: pczwl@exmail.nottingham.ac.uk

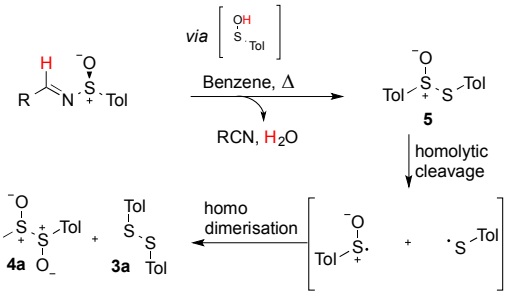
have an effect on the generality of this transformation (Table 1). The observed transformation proves to be general to a range of sulfinimines bearing either aryl or alkyl group affording the above mentioned disulfoxide in moderate yields (Table 1, entries 1-5). Furthermore, the sulfinimine bearing a mesityl group on the sulfur atom led to the corresponding mesityldisulfoxide albeit in lower yield, presumably due to instability of this compound in solution (Table 1, entry 6), whereas the corresponding *tert*-butyl substituted sulfinimine did not (Table 2, entry 7).

Thermal degradation of sufinimines was reported by Davis *et al.* in 1974 for the thermolysis of *N*-alkylidenarenesulfinamides[6] although, based on previously reported studies,[7] they proposed the corresponding disulfide and thiolsulfonate as reaction products. Davis' pioneering work presents the formation of the corresponding nitrile by a Cope-type elimination, giving rise to arylsulfenic acid that undergoes dimerisation to generate a thiolsulfinate intermediate that then disproportionates to disulfide **3a** and thiosulfonate **2a** products (Scheme 1a). Davis was able to trap the sulfenic acid intermediates but were unable to isolate the thiolsulfinate. To test whether our transformation proceeds through a mechanistic pathway similar to the one described previously by Davis, we carried out a series of control experiments (Scheme 2).



Scheme 2. Control experiments.

We synthesised the thiolsulfinate **5**, suggested by Davis as an intermediate towards the formation of thiolsulfonate **2a**, and immediately submitted it to the optimised reaction conditions. In our hands disulfoxide **4a** and disulfide **3a** were given as products of this transformation. We also wanted to confirm the involvement of radical species in our transformation. To that end, we carried out the transformation in the presence of the radical inhibitor butylated hydroxytoluene (BHT) and observed the formation of compounds **3a** and **4a** in slightly lower yields, although no products of radical trapping were isolated.[8] Experiments involving amine **1'ab** and ketimine **1''ab**, and the isolation of the non volatile 2-naphthonitrile (Table 1, entry 3), let us to propose a mechanism that implies initial formation of thiolsulfinate **5**, *via* tolylsulfenic acid, through a Cope type elimination, in agreement with Davis seminal report.[6] Then homolytic cleaveage of S-S bond and subsequent recombination of the radical pair takes place inside the solvent cage to generate the disulfoxide and its reduced counterpart[9] (Scheme 3).



Scheme 3. Proposed mechanism of diulfoxide formation.

1,2-Disulfoxides have been broadly studied due to their involvement as intermediates in important biological processes[10] and their use as ligands in metal catalysed transformations.[11] 1,2-Disulfoxides have been characterised as unstable, non isolable compounds that tend to isomerise to the corresponding thiolsulfonate.[121] Hitherto, only cyclic 1,2-disulfoxides have been isolated and their structure studied by X-Ray analysis.[13] (Figure 1).

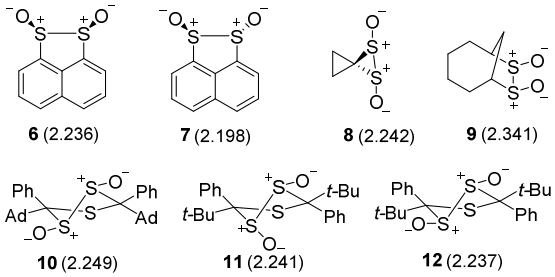


Figure 1. Previously isolated disulfoxides. In brackets S-S bond length in Å.

At this point we turned our attention towards the study of the structure of the isolated disulfoxide. Attending to the spectroscopic data, 1,2-disulfoxide is isolated from our reaction conditions as a stochastic mixture of diastereomers. Racemic C_2 symmetric disulfoxide, (*R*,*R*)-**4a** (and its antipode), and the meso compound were identified by ^{1}H-NMR and ^{13}C-NMR spectroscopy. Isolation of suitable crystals allowed us to perform X-Ray diffraction analysis although just the meso compound afforded crystals suitable for the above mentioned analysis (Figure 2). For comparative purposes, already known disulfide **3a**

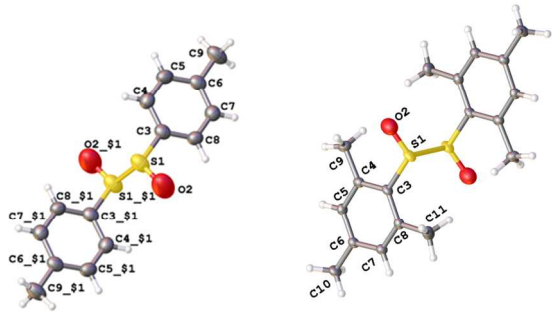


Figure 2. X-Ray structures of disulfoxide **4a** and **4b**.

was crystallised and analysed under the same conditions.[13]

The compound meso-**4a** has a bond length between the sulfur atoms of 2.110 Å, the sulfur oxygen bond is 1.261 Å with a O-S-S-O dihedral angle of 180º to minimise dipole repulsion. Comparing to related disulfoxides, disulfoxide **4a** presents a shorter bond distance between sulfur atoms that could explain the unusual stability observed for our compound. Calculations previously reported on similar substrates predicted the same spatial disposition in order to minimise the dipole-dipole interaction together with a bond length for the S-S bond of 2.30 Å.

As previously observed for disulfoxide **4a**, although **4b** was isolated as a mixture of *rac*-(*R*,*R*)-**4b** and meso **4b**, only the non chiral molecule afford crystals suitable for X-Ray analysis. Compared to the analogous **4a**, the more electron rich disulfoxide **4b** bears a longer sulfur-sulfur bond length of 2.128 Å and a sulfur-oxygen atom distance of 1.392 Å. The longer sulfur-sulfur distance could be explained by the lower electron withdrawing effect of mesityl group, compared to tolyl, on the sulfur atom and could also be an explanation for the lower stability in solution noticed for this compound. Furthermore, the two oxygen atoms in the molecule display an antiplanar disposition in order to minimise dipole-dipole repulsion (O-S-S-O dihedral angle of 180º). Our results show again that such instability was overestimated and vicinal disulfoxides are the actual compound obtained, together with disulfide and the corresponding nitrile, on the thermal decomposition of sulfinimines.

Conclusions

We have unambiguously confirmed the structure of the products obtained from the thermolysis of sulfinimines as vicinal sulfoxides. Furthermore the isolation and characterisation of these novel species opens the door to studies of the reactivity of these structures and the design and synthesis of new ligands for transition metals. Studies along these lines are ongoing in our laboratories.

Acknowledgments

Xunta de Galicia (JAS), University of Nottingham and EPSRC (EP/E055346) are acknowledged for funding.

Notes and references

1 (a) F. A. Davis, R. E. Reddy, J. M. Szewezyk, P. Portonovo, *Tetrahedon Lett.*, 1993, **34**, 6229; (b) F. A. Davis, R. E. Reddy, J. M. Szewezyk, G. V. Reddy, P. S. Portonovo, H. Zhang, D. Fanelli, R. Thimma Reddy, P. Zhou, P. J. Carroll *J. Org. Chem.*, 1997, **62**, 2555; (c) F. A. Davis, Y. Zhang, Y. Andemichael, T Fang, D. L. Fanelli, H. Zhang, *J. Org. Chem.*, 1999, **64**, 1403; (d) D. L. Fanelli, J. M. Szewezyk, Y. Zhang, G. V. Reddy, D. M. Burns, F. A. Davis *Org. Synth.*, 1999, **77**, 50.

2 M. T. Robak, M. A. Herbage, J. A. Ellman, *Chem. Rev.*, 2010, **110**, 3600 and the references cited therein.

3 (a) D. Morton, D. Pearson, R. A. Field, R. A. Stockman, *Synlett*, 2003, 1985; (b) L. G. Arini, A. Sinclair, P. Szeto, R. A. Stockman, *Tetrahedron Lett.,* 2004, **45**, 1589; (c) D. Morton, D. Pearson, R. A. Field, R. A. Stockman, *Org. Lett.,* 2004, **6**, 2377; (d) D. Morton, D. Pearson, R. A. Field and R. A. Stockman, *Chem. Commun.* 2006, 1833; (e) D. Morton, R. A. Stockman, *Tetrahedron,* 2006, **62**, 8869; (f) K. Chigboh, A. Nadin, R. A. Stockman, *Synlett*, 2007, 2879; (g) D. Morton, A. Nadin, R. A. Stockman, *Tetrahedron Lett.*, 2008, **49**, 4768; (h) D. C. Forbes, S. V. Bettigeri, S. R. Amin, C. J. Bean, A. M. Law, R. A. Stockman *Synth. Comm.*, 2009, **39**, 2405; (i) C. Roe, T. Moragas-Sola, L. Sasraku-Neequye, H. Hobbs, I. Churcher, D. MacPherson, R. A. Stockman, *Chem. Commun.,* 2011, 4791; (j) T. Moragas-Sola, I. Churcher, R. A. Stockman, *Org. Biomol Chem.*, 2011, **9**, 5034; (k) G. Procopiou, W. Lewis, G. Harbottle, R. A. Stockman, *Org. Lett.*, 2013, **15**, 2030. (l) E. M. Rochette, W. Lewis, A. G. Dossetter, R. A. Stockman, *Chem. Commun.*, 2013, **49**, 9395.

4 For selected examples of aza Diels-Alder reactions of sulfinimines, see: (a) F. Palacios, J. Vicario, D. Aparicio, *Tetrahedron Lett.*, 2007, **48**, 6747; (b) S. Kobayashi, T. Furuya, T. Otani, T. Saito, *Tetrahedron*, 2008, **64**, 9705; (c) P. Li, L-J. Liu, J-T. Liu, *Org. Biomol. Chem.*, 2011, **9**, 74.

5 See ESI for further details on the solvents screening.

6 F. A. Davis, A. J. Friedman, E. W. Kluger, *J. Am. Chem. Soc.*, 1974, **96**, 5000.

7 (a) S. Oae, R. Nomara, Y. Yoshikawa, W. Tabaki, *Bull. Chem. Soc. Jap.*, 1969, **42**, 2903. (b) P. Koch, E. Ciuffarin, A. Fava, *J. Am. Chem. Soc.*, 1971, **92**, 5971 (Note, this citation was incorrect in ref 5). (c) D. Barnard, , *J. Chem. Soc.*, 1957, 4675.

8 Geminate recombination of radicals is well know and has been previously documented. (a) R. K. Lyon, D. H. Levy, *J. Am. Chem. Soc.* 1961, **83**, 4290. (b) R. K. Lyon, *J. Am. Chem. Soc.* 1964, **86**, 1907 (c) J. W. Taylor, J. C. Martin, *J. Am. Chem. Soc.* 1966, **88**, 3650 (d). J. W. Taylor, J. C. Martin, *J. Am. Chem. Soc.* 1967, **89**, 6904.

9 A similar suggestion, involving the intervention of solvent, has been made in the computational study of the isomerisation of sulfenylsulfinates to thiosulfonate carried out by Gregory and Jenks. D. D. Gregory, W. S. Jenks, *J. Phys. Chem. A*, 2003, **107**, 3414.

10 (a) G. Medes, *Biochem. J*,. 1937, **31**, 1330; (b) G. Medes, N. Floyd, *Biochem. J.*, 1942, **36**, 259.

11 (a) M. S. Chen, N. Prabagaran, N. A. Labenz, M. C. White, *J. Am. Chem. Soc.*, 2005, **127**, 6970; (b) M. S. Chen, M. C. White, *J. Am. Chem. Soc*, 2004, **126**, 1346; (c) J. H. Delcamp, P. E. Gormisky, M. C. White, *J. Am. Chem. Soc*, 2013, **135**, 8460; (d) K. J.; Fraunhoffer, M. C. White, *J. Am. Chem. Soc*, 2007, **129**, 7274; (e) S. A. Reed, M. C. White, *J. Am. Chem. Soc*, 2008, **130**, 3316; (f) , E. M. Stang, M. C. White, *J. Am. Chem. Soc*, 2011, **133**, 14892; (g) A. J. Young, M. C. White, *J. Am. Chem. Soc*, 2008, **130**, 14090.

12 For selected studies on the reactivity of 1,2-disulfoxides, see: (a) F. Freeman, *Chemical Reviews* 1984, **84**, 117; (b) M. M. Chau, J. L. Kice, *J. Am. Chem. Soc*, 1976, **98**, 7711; (c) F. Freeman, C. N. Angeletakis, *J. Am. Chem. Soc*, 1982, **104**, 5766; (d) F. Freeman, C. N. Angeletakis, *J. Am. Chem. Soc*, 1983, **105**, 4039; (e) F. Freeman, C. N. Angeletakis, T. Maricich, *J. Am. Chem. Soc*, 1981, **103**, 6232; (f) F. Freeman, C. N. Angeletakis, W. J. Pietro, W. J. Hehre, *J. Am. Chem. Soc*, 1982, **104**, 1161.

13 (a) A. Ishii, M. Nakabayashi, J. Nakayama, *J. Am. Chem. Soc*, 1999, **121**, 7959; (b) A. Ishii, M. Nakabayashi, Y.-N. Jin, J. Nakayama, *J. Organometallic Chem.*. 2000, **611**, 127; (c) H. Oshida, A. Ishii, J. Nakayama, *Tetrahedron Letters*, 2002, **43**, 5033; (d) H. Oshida, A. Ishii, J. Nakayama, *J. Org. CheM.i,* 2004, **69**, 1695; (e) A. Ishii, S. Kashiura, H. Oshida, J. Nakayama, *Org. Lett.,* 2004, **6**, 2623; (f) A. Ishii, M. Ohishi, K. Matsumoto, T. Takayanagi, *Org. Lett.,* 2005, **8**, 91; (g) A. Ishii, M. Ohishi, N. Nakata, *Eur. J. Inorg Chem.*, 2007, 5199; (h) R. S. Grainger, B. Patel, B. M. Kariuki, *Angew. Chem. Int. Ed.*, 2009, **48**, 4832.

14 See ESI for further details