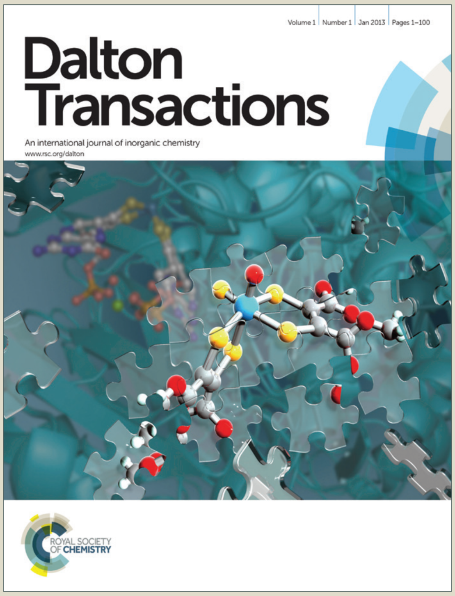
Dalton Transactions

Accepted Manuscript



Volume 1 | Number 1 | Jan 2013 | Pages 1–100

Dalton Transactions

An international journal of inorganic chemistry

www.rsc.org/dalton

ROYAL SOCIETY OF CHEMISTRY

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/dalton

Dalton Transactions

Dynamic Article Links ►

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

COMMUNICATION

Copper-promoted aerial oxidation of benzothiadiazines: Access to benzothiadiazine S-oxide heterocycles.

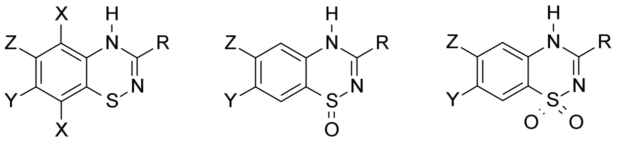
Ewan R. Clark,[a] John J. Hayward,[b] Bryce J. Leontowicz,[b] Muhammad U. Anwar,[b] Melanie Pilkington,[c] and Jeremy M. Rawson*[a,b]

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

DOI: 10.1039/b000000x

Cu^{2+}-promoted aerial oxidation of a series of benzothiadiazines (1) under ambient conditions affords the first structurally characterised examples of thiadiazine S-oxides (2) The isolation of the homoleptic Cu^{II} 3-(2′-pyridyl)benzothiadiazide-S-oxide complex provides insight into the reaction mechanism.

The family of (benzo)-1,2,4-thiadiazines with sulfur in various oxidation states (Scheme 1, **1** – **3**) has attracted attention for both materials and pharmaceuticals applications:[1-5] The one electron oxidation of **1** (X = Y = Z =H) was first reported in the 1980s to afford persistent radicals.[1] Halogenated derivatives (X = Y = Z =F, Cl; R = Ph) are sufficiently stable to afford their isolation by chromatography[2] and alkylated derivatives (Y = $^{n}C_6H_{13}O$; R = *p*-$C_4H_9OC_6H_4$) found to exhibit liquid crystalline properties.[3] Resonance-stabilized bis(thiadiazines) (R = H, Ph, thienyl) and related species have also attracted attention as conducting materials.[4] The thiadiazine-*S*,*S*-dioxide structure **3** has been widely studied and is central to a range of commercially available pharmaceuticals, classified as thiazide drugs (such as chlorothiazides R = H, CH_2Cl; Y = SO_2NH_2, Z = Cl) which are diuretics and have applications for the treatment of hypertension, osteoporosis and hyperglycemia.[5] Conversely the *S*-oxide **2** has barely been investigated with just one directed synthesis described (Y = Cl, Br, SO_2NH_2; Z = H, NO_2; R = Ar, PhNH, Me_2N, MeS, CF_3)[6] and, to the best of our knowledge, there are no crystallographic studies on **2** to date.

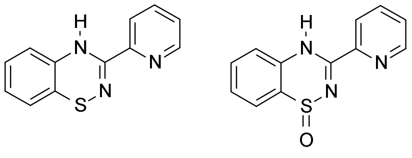


1 **2** **3**

Scheme 1 Benzothiadiazines containing S^{II} (**1**), S^{IV} (**2**) and S^{VI} (**3**) centres.

Classically, interconversion from sulfide to sulfoxide to sulfone relies on careful control of the oxidizing agent. Notably, the conversion of sulfides to sulfoxides is conventionally achieved using stoichiometric quantities of strong oxidants such as peracids, high oxidation state metals (such as MnO_2 and CrO_3) or oxidizing non-metal species such as IO_4^- or PhIO so as to avoid over-oxidation.[7] Similarly, oxidation of **2** to **3** was achieved under quite harsh conditions (35% H_2O_2 at 100 °C in glacial acetic acid) in moderate yields (39 – 72 %).[6b] Indeed, the resistance of **1** to oxidation is reflected in its reactivity with PbO_2 or the stronger oxidant AgO which only affords the benzothiadiazinyl radical *via* H-atom abstraction rather than the *S*-oxide or *S*,*S*-dioxide.[1-3] In this study we report the metal-catalysed aerial oxidation of **1** to **2** under mild conditions together with the first structure determinations of **2** in which we observe that the *S*-oxide acts as a strong hydrogen-bond acceptor and unambiguously determine the site of N-H protonation (*i.e.* tautomeric form **2**).

Our foray into this area stemmed from our recent studies on the synthesis[8] and coordination chemistry[9] of the 3-(2′-pyridyl) benzothiadiazine ligand **L₁**H (Scheme 2). The synthesis of a range of first row transition metal complexes (containing VO^{2+}, Mn^{2+},Fe^{2+}, Co^{2+} and Zn^{2+}) proved straight forward under aerobic conditions, affording complexes of **L₁**H where the ligand remained protonated. In order to probe the acidity of this N-H group, we treated a methanolic solution of $Cu(\mathbf{L_1}H)_2Cl_2$ with Et_3N and noted a rapid colour change from red to green. Recrystallisation of the green solution obtained under aerobic conditions unexpectedly afforded dark green crystals of the homoleptic dimeric Cu^{II} complex, $[Cu(\mathbf{L_2})_2]_2$ (**4**) in which the neutral ligand **L₁**H had been simultaneoulsy oxidized and deprotonated to form the anion $\mathbf{L_2}^-$.§



L₁H **L₂**H

Scheme 2

The structure of **4** was determined by X-ray diffraction‡ (Fig. 2) and crystallises in the triclinic space group *P*-1. The two Cu^{II} centres within **4** are related *via* an inversion centre with each copper centre adopting a 5-coordinate geometry with an N_4O donor set. The Addison τ value[10] (0.89) is consistent with a geometry close to trigonal pyramidal (τ = 1 for trigonal pyramidal and 0 for square pyramidal) with N(1)Cu(1)N(4) = 175.90(14)^{o} defining the axial orientation with the remaining angles in the equatorial plane in the range 114.98(13) – 122.52(13)^{o}. Notably, the two crystallographically independent $\mathbf{L_2}^-$ anions adopt different coordination modes. The first adopts a simple N,N′-chelate mode to a single Cu(1) centre in which the pyridyl N(1) and the heterocyclic N(2) atoms are involved in metal binding in an analogous fashion to $\mathbf{L_1}$H. In comparison, the second crystallographically independent $\mathbf{L_2}^-$ anion takes up a bridging mode between two Cu^{II} centres. For this second ligand N(4) (located across the heterocyclic ring from S) and the pyridyl N(3) atom chelate one Cu(II) centre and the S-oxide O(2) bridges to the second Cu(II) centre. This is markedly different from the previous coordination complexes of $\mathbf{L_1}$H where invariably N(2) and the pyridyl N act as the N,N′-chelate. Thus S-oxidation seems to reduce the coordinating strength of N(2) and enhance the donor ability of the deprotonated N(4) atom. The S-O bonds in both terminal and bridging $\mathbf{L_2}^-$ anions are identical at 1.501(4) Å, and comparable with other literature reported sulfoxide bonds (av. 1.49 Å).[11]

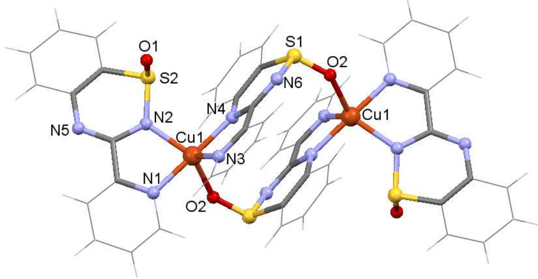
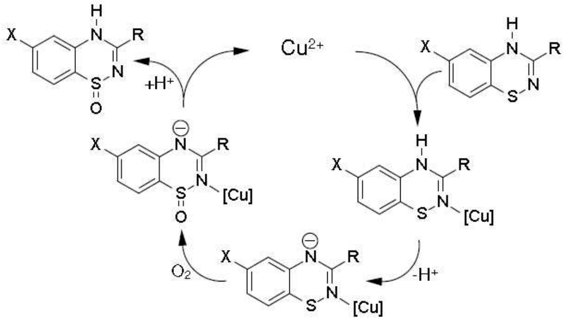


Fig. 1 Crystal structure of **4** with solvent molecules omitted for clarity.

The initial isolation of $CuCl_2(\mathbf{L_1}H)_2$ and conversion to $[Cu(\mathbf{L_2})_2]_2$ after addition of Et_3N (promoting H^+ abstraction), suggested the potential to develop a catalytic cycle (Scheme 3) in which the Lewis acidic Cu^{2+} ion would appear to activate both the N-H group to deprotonation and the S centre to oxidation. Since S-oxidation of $Cu(\mathbf{L_1})_2Cl_2$ does not occur in the absence of Et_3N then deprotonation of coordinated $\mathbf{L_1}$H appears to be rate determining. Such Lewis-acid catalysed S-oxidation is not without precedent; in recent years, Li *et al.*, have shown that *m*CPBA can oxidise thiophene to its corresponding S-oxide in the presence of $BF_3{\cdot}Et_2O$,[12] whilst the high Lewis acidity of the peroxotungstate ion has been implicated in the catalytic oxidation of organic sulfides with H_2O_2.[13] In order to complete the catalytic cycle, the deprotonated benzothiadiazine *S*-oxide ligand must be liberated to regenerate Cu^{2+}. We therefore pursued other derivatives of **1**, in which the 2′-pyridyl ring was replaced with non-coordinating phenyl or 2′-thiophenyl rings (**1a** – **1c**, Scheme 3) affording more weakly coordinating monodentate donor substrates.

All three substrates **1a** – **1c** underwent aerial oxidation in the presence of stoichiometric ($\mathbf{L_1}H{:}Cu^{2+}{=}2{:}1$) and sub-stoichiometric ($\mathbf{L_1}H{:}Cu^{2+}{=}20{:}1$) quantities of Cu^{2+} to form the corresponding *S*-oxide (Scheme 3) at room temperature over 1 week with a concommitant decolourisation of the solution. Notably, samples stored (i) in the absence of $CuCl_2$ but open to air, or (ii) in the presence of $CuCl_2$ but in the absence of oxygen (degassed solutions in sealed vessels) showed no tendency to decolourise. The corresponding benzothiadiazine *S*-oxides **2a** – **2c** were obtained in analytically pure crystalline form in 57 – 81 % (unoptimised recovered yields) by simple filtration from the mother liquor (see ESI). Sulfoxides typically exhibit a strong $\nu_{S=O}$ in the IR (1070 – 1030 cm^{-1}).[14] The *S*-oxides **2a** – **2c** all exhibit $\nu_{S=O}$ at *ca.* 1000 cm^{-1}, a feature absent in **1a** – **1c**, consistent with the presence of both conjugation and hydrogen-bonding (*vide infra*).[14] These compounds also provided satisfactory elemental analysis, ESI MS and ^{1}H NMR spectra. The molecular structures of **2a** – **2c** (Figure 2) were determined by X-ray diffraction‡



(a) X = H, R = Ph; (b) X= H, R = 2-thienyl; (c) X = CF_3 R = Ph

Scheme 3 Catalytic cycle for the conversion of **1** to **2**.

When comparing **1a** – **1c**[8] with **2a** – **2c**, a marked shortening of the S-N bond by approximately 0.06 Å (from *ca.* 1.72 to *ca.* 1.66 Å) is observed. Other changes are less than 0.02 Å and often the same within error (3 esd's). The *S*-oxide bonds, which fall in the range 1.498(1) – 1.508(2) Å, are comparable with other formal *S*-oxides.[11] Two possible tautomers exist for **2**, depending on whether the N(2) or N(4) atom is protonated; whilst Kresze[6a] proposed protonation at N(2), Finch[6b] favoured the tautomer with protonation at N(4). Our structural studies located the H atom positions at N(4) in all cases and this assignment was further supported by shorter imine-like C-N(2) and longer C-N(4) bonds. The *S*-oxide moiety appears to be an efficient hydrogen-bond acceptor and all three structures exhibit N-H···O-S hydrogen-bonds, further confirming protonation at N(4). This hydrogen bonding is manifested in formation of a centrosymmetric dimer (**2b**) or one-dimensional chain motifs (**2a** and **2c**) (see ESI).

This synthetic methodology provides an alternative strategy to that developed by Finch *et al.*[6c] which incorporates the S^{IV} centre prior to ring closure. The current approach provides a stepwise interconversion between **1** and **2** after ring closure. In this context Kresze and coworkers showed[6b] that oxidation of **2** to **3** can be achieved with 35% H_2O_2 in glacial acetic acid and our current contribution thus provides a pathway for interconversion from **1** to **2** to **3**. Notably the reverse transformation, **2** to **1**, seems more problematic; Kresze found that conversion of **2** to **1** could be achieved using $SOCl_2$ but was accompanied by chlorination at the benzo-ring.[6b] Finch also converted **2** to **1** through Bu_3P reduction but this reaction was hampered by ring contraction to the benzothiazole if reaction conditions were not carefully controlled.[6c]

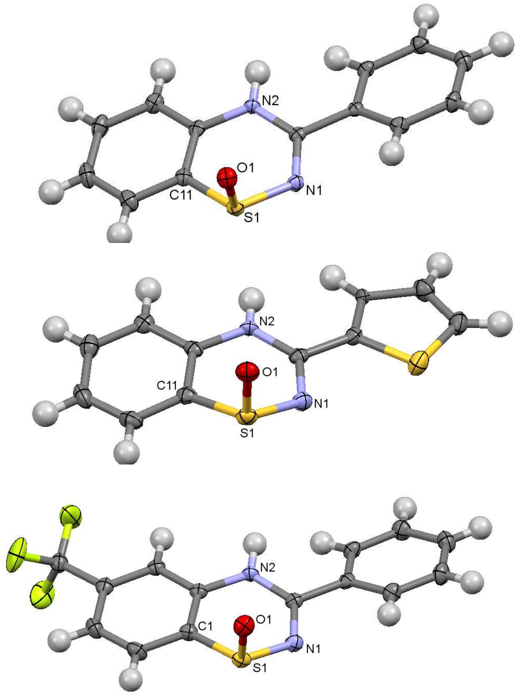


Fig.2 Crystal structures of **2a** – **2c** with thermal ellipsoids plotted at the 50 % probability level.

To summarize, benzothiadiazine *S*-oxides can be prepared *via* the aerial oxidation of benzothiadiazines employing Lewis-acidic Cu^{II} ions and permitted us to structurally characterise the first benzothiadiazine *S*-oxides, **2a** – **2c**. It is likely that other Lewis acids may also catalyse this process. With derivatives of **2** now in hand, we are well-placed to explore the chemistry and biological properties of this largely unexplored heterocyclic ring system, the results of which will be published in due course.

Acknowledgements. We thank the EPSRC for studentship (E.R.C.) and the Canada Research Chair program for funding (J.M.R. and M.P.) and Dr. J.E. Davies for collecting crystallographic data on **4**.

Notes and references

[a] *Department of Chemistry, The University of Cambridge, Lensfield Road, Cambridge UK CB2 1EW.*
[b] *Department of Chemistry and Biochemistry, The University of Windsor, 401 Sunset Avenue, Windsor ON, Canada N9B 3P4.; E-mail: jmrawson@uwindsor.ca*
[c] *Department of Chemistry, Brock University, 500 Glenridge Ave., St Catharines, ON, Canada L2S 3A1.*

† Electronic Supplementary Information (ESI) available: Full synthetic details and characterisation of complex **4** and benzothiadiazine S-oxides **2a** – **2c**, crystal packing of **2a** – **2c** and crystallographic files in cif format. See DOI: 10.1039/b000000x/

§ Preparation of complex **4**. A solution of $\mathbf{L_1}$H (180 mg, 0.79 mmol) in MeOH (50 mL) was added to $CuCl_2{\cdot}2H_2O$ (0.102g, 0.42 mmol) dissolved in MeOH (20 mL) to afford a red solution. On addition of Et_3N a rapid colour change from red to green was observed. After 48h the volume was reduced until a green precipitate began to form. The solution was then filtered, after which slow evaporation afforded green needle crystals of **4** which were isolated by filtration and washed with MeOH (10 mL) and hexane (10 mL) and dried *in vacuo*. Yield 156 mg (68%) Calc. for **4**·MeOH C 51.8, H 3.5, N 14.5%, found C 51.0, H 3.5, N 14.1%.

Preparation of **2a** – **2c**. In a typical reaction crystalline **1** (0.8 mmol) was added to a solution of $CuCl_2$ (54 mg, 0.4 mmol or 5.4 mg, 0.04 mmol) in MeOH to form a clear orange solution. The solution was stored for up to 8 days during which time the solution became pale and crystals of **2** formed which were isolated by filtration washed with MeOH (10 mL) and hexane (10 mL) and dried *in vacuo*. Yields: **2a**: 110 mg, 57%; **2b**: 129 mg, 65%; **2c** 200 mg, 81%. See ESI for analytical data for **2a** – **2c**.

‡ Crystallographic data: Compound **4**·MeOH $C_{24}H_{16}CuN_6O_2S_2$ (CH_3OH), M = 580.13, Triclinic, space group P-1, $Z = 2$, $a = 8.9974(18)$, $b = 10.434(2)$, $c = 14.204(3)$ Å, $\alpha = 75.65(3)$, $\beta = 88.65(3)$, $\gamma = 68.44(3)^o$, $V = 1198.1(4)$ Å^3, μ(Mo-Kα) = 1.128 mm^{-1}, $\rho_{calc} = 1.608$ Mg m^{-3}, T = 200(2) K. total reflections 11353, 3124 unique ($R_{int} = 0.040$), $R_1 = 0.042$ ($I > 2\sigma(I)$), $wR_2 = 0.111$ (all data). Compound **2a** $C_{13}H_{10}N_2OS$, M = 242.29, Orthorhombic, space group $Pbca$, $Z = 8$, $a = 8.4577(5)$, $b = 11.9926(7)$, $c = 21.3438(13)$ Å, $V = 2164.9(2)$ Å^3, μ(Mo-Kα) = 0.281 mm^{-1}, ρ_{calc} = 1.487 Mg m^{-3}, T = 150(2) K. total reflections 10187, 1904 unique ($R_{int} = 0.032$), $R_1 = 0.044$ ($I > 2\sigma(I)$), $wR_2 = 0.112$ (all data). Compound **2b** $C_{11}H_8N_2OS_2$, M = 248.31, Monoclinic, space group $P2_1/c$, $Z = 4$, $a = 8.2057(5)$, $b = 18.0582(12)$, $c = 7.4221(4)$ Å, $\beta = 111.185(3)^o$, $V = 1025.48(11)$ Å^3, μ(Mo-Kα) = 0.494 mm^{-1}, ρ_{calc} = 1.608 Mg m^{-3}, T = 150(2) K. total reflections 8216, 1808 unique ($R_{int} = 0.028$), $R_1 = 0.040$ ($I > 2\sigma(I)$), $wR_2 = 0.095$ (all data). Compound **2c** $C_{14}H_9F_3N_2OS$, M = 310.29, Monoclinic, space group $P2_1/c$, $Z = 4$, $a = 12.7488(9)$, $b = 8.6205(6)$, $c = 12.1309(8)$ Å, $\beta = 101.918(3)^o$, $V = 1304.46(16)$ Å^3, μ(Mo-Kα) = 0.284 mm^{-1}, ρ_{calc} = 1.580 Mg m^{-3}, T = 150(2) K. total reflections 19374, 2303 unique ($R_{int} = 0.029$), $R_1 = 0.035$ ($I > 2\sigma(I)$), $wR_2 = 0.087$ (all data). CCDC deposit numbers: 1027456-1027459.

1 (a) L.N. Markovskii, V.S. Talanov, O.M. Polumbrik and Y.G. Shermolovich, *J. Org. Chem. USSR*, 1981, **17**, 2338; (b) Y.G. Shermolovich, Y.A. Simonov, A.A. Dvorkin, O.M. Polumbrik, G.S. Borovikova, E.I. Kaminskaya, E.S. Levchenko and L.N. Markovskii, *Russ. J. Org. Chem.*, 1989, **25**, 550.

2 J. Zienkiewicz, P. Kaszynski and V. G. Young, Jr., *J. Org. Chem.*, 2004, **69**, 7525.

3 J. Zienkiewicz, A. Fryszkowska, K. Zienkiewicz, F. Guo, P. Kaszynski, A. Januszko and D. Jones, *J. Org. Chem.* 2007, **72**, 3510.

4 L. Beer, R. C. Haddon, M. E. Itkis, A. A. Leitch, R. T. Oakley, R. W. Reed, J. F. Richardson and D. G. VanderVeer, *Chem. Commun.*, 2005, 1218; A. A. Leitch, R. T. Oakley, R. W. Reed and L. K. Thompson, *Inorg. Chem.*, 2007, **46**, 6261; S. M. Winter, A. R. Balo, R. J. Roberts, K. Lekin, A. Assoud, P. A. Dube and R. T. Oakley, *Chem. Commun.*, 2013, **49**, 1603.

5 See for example: (a) F.C. Novello, and J.M. Sprague, *J. Am. Chem. Soc.*, 1957, **79**, 2028; (b) P. G. Welling, *Biopharm. Drug Dispos.*, 1986, **7**, 501; (c) S.S. Fajans, J.C. Floyd Jr., R.F. Knopf, J. Rull, E.M. Guntsche and J.W. Conn, *J. Clin. Investgn.*, 1966, **45**, 481; (d) A. Fretheim, *BMC Family Practice*, 2003, **4**, 19.

6 (a) G. Kresze, C. Seyfried and A. Trede, *Tetrahedron Lett.*, 1965, **6**, 3933; (b) G. Kresze, C. Seyfried and A. Trede, *Liebigs. Ann. Chem.* 1968, **715**, 223; (c) N. Finch, S. Ricca, Jr., L. H. Werner and R. Rodebaugh, *J. Org. Chem.*, 1980, **45**, 3416; (d) D. D. Ross and D. Lednicer, *J. Het. Chem.*, 1982, **19**, 975; (e) E. S. Levchenko, G. S. Borovikova, E. I. Borovik and V. N. Kalinin, *Z. Organisch. Khim.*, 1984, **20**, 196.

7 For example: (a) K. Kaczorowska, Z. Kolarska, K. Mitka and P. Kowalski, *Tetrahedron*, 2005, **61**, 8315; (b) *Modern Oxidation Methods*, J.-E. Bäckvall Ed., Wiley-VCH, Weinheim, 2004, 193.

8 E. R. Clark, J. J. Hayward, B. J. Leontowicz, D. J. Eisler and J. M. Rawson, *CrystEngComm.*, 2014, **16**, 1755.

9 E. R. Clark, M. U. Anwar, B. J. Leontowicz, Y. Beldjoudi, J. J. Hayward, W. T. K. Chan, E. L. Gavey, M. Pilkington, E. Zysman-Colman and J. M. Rawson, *Dalton Trans.*, 2014, **43**, 12996.

10 A.W. Addison, T.N. Rao, J. Reedijk, J. van Rijn and G.C. Verschoor, *J. Chem. Soc. Dalton Trans.*, 1984, 1349.

11 M. Calligaris, *Croat. Chim. Acta*, 1999, **72**, 147.

12 Y. Li, T. Thiemann, T. Sawada, S. Mataka and M. Tashiro, *J. Org. Chem.* 1997, **62**, 7926.

13 K. Kamata, T. Hirano and N. Mizuno, *Chem. Commun.*, 2009, 3958.

14 *Spectroscopic Identification of Organic Compounds*, 4th Edition, R.M. Silverstein, G.C. Bassler and T.C. Morrill, J. Wiley, 1981.

Table of Contents

Copper-promoted aerial oxidation of benzothiadiazines: Access to benzothiadiazine S-oxide heterocycles.

Ewan R. Clark, John J. Hayward, Bryce J. Leontowicz, Muhammad U. Anwar, Melanie Pilkington and Jeremy M. Rawson

Dalton Trans., 2014, xxx
DOI: 10.1039/xxxxxxxx

Aerial oxidation of benzothiadiazines selectively affords the corresponding benzothiadiazine S-oxides in the presence of Cu^{2+} ions. Structural studies reveal that the S-oxide appears to be a strong hydrogen-bond acceptor.