

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

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Electronic Supplementary Information

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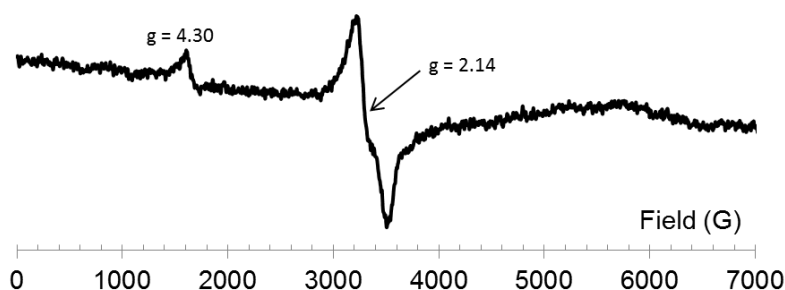
SUP-1: General Experimental Considerations.

Compounds **1a** – **1c** were prepared according to the literature method [1]. Brown, anhydrous CuCl_2 was prepared by dehydrating $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ by heating *in vacuo* at 130 °C, all solvents were used without further purification unless otherwise indicated. NMR spectra were recorded on a Bruker Avance 300US or a Bruker 500 MHz Avance III with a BBFO probe with residual solvent peaks used as internal standards; coupling constants were measured directly from the spectra and were not averaged. Electron Impact mass spectrometry was performed on a Kratos MS890-EI mass spectrometer; Electrospray Mass Spectrometry was performed using a Waters LTC machine or Waters Micromass LCT Classic (ESI-TOF) Mass Spectrometer. Elemental analyses were recorded on a PerkinElmer 2400 Series II Elemental Analyzer. Melting points were determined using a Stanford Research Systems MPA120 EZ-Melt Automated Melting Point Apparatus. IR spectra were recorded as thin films on a Bruker Alpha FT-IR equipped with a Platinum single reflection diamond ATR module. Details of crystallographic studies are presented in SUP-7.

SUP-2: Synthesis of Complex **4**

A solution of L_1H (0.180g, 0.79 mmol) in MeOH (50 mL) was added to $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (0.102g, 0.42 mmol) dissolved in MeOH (20 mL) to afford a red solution. Addition of excess Et_3N (4.3 mL, 42 mmol) led to a rapid colour change from red to green upon air exposure. After 48h the volume was reduced until a green precipitate just began to form. The solution was then filtered and green needle crystals of **4** formed upon slow evaporation which were washed with MeOH (10 mL) and hexane (10 mL) and dried *in vacuo*. Yield 0.156 g (68%). **mp** 297 °C. Calc. for **4**·MeOH C 51.8, H 3.5, N 14.5%, found C 51.0, H 3.5, N 14.1%. **IR** (solid, $\nu_{\text{max}}/\text{cm}^{-1}$): 3440 br (N-H), 1605 m (C=N), 1508 s, 1520 s, 1505 s, 1495 s, 1475 s, 1455 s, 1429 br, 1383 s, 1288 m, 1274 s, 1259 s, 1149 m, 1134 s, 1095 br, 1051 m, 1078 s, 985 br (S=O), 926 m, 828 m, 810 m, 791 s, 762 s, 748 s, 731 s, 679 s, 655 m, 642 s, 598 s, 560 s, 530 s, 479 s, 442 s, 411 m.

The solid state EPR spectrum of **4** (Bruker EMXplus EPRspectrometer, room temperature, $\nu = 9.85473$ GHz) comprises a feature around $g = 2.14$ and a weaker feature around $g = 4.30$ consistent with a Cu^{II} dimer with the lower field resonance consistent with the spin-forbidden $\Delta M_S = 2$ transition associated with a triplet state.



SUP-3: Copper-Promoted Oxidation Reactions.

In a typical reaction CuCl_2 was dissolved in MeOH and solid **1** (0.8 mmol) added, the orange solution was stirred briefly and then allowed to stand at room temperature. Over 1 – 15 d the solution decolourised to afford pale yellow/white crystals of **2** which were isolated by filtration, washed with MeOH (10 mL) and hexane (10 mL) and dried *in vacuo*. Details of reaction conditions implemented are given in Table S1, analytical data for **2a** – **2c** are given in SUP-4, SUP-5 and SUP-6.

No decolorisation of the solution occurred in the absence of Cu^{2+} ions or when solvent was thoroughly degassed and the reaction mixture stored under nitrogen. In such cases when the system was subsequently released to air, reaction proceeded and the solution slowly decolorised.

Table S1. Reaction conditions and yields for Cu^{2+} promoted oxidation of **1** (an ‘open vessel’ reflects a flask with perforated parafilm to permit O_2 diffusion but avoiding contamination with particulates).

Substrate	Amount	1 : Cu^{2+}	Conditions	Yield of 2
1a	181 mg, 0.8 mmol	--	Open vessel, 18 mL non-degassed MeOH, 12d	--
1a	181 mg, 0.8 mmol	20:1	Open vessel, 14 mL non-degassed MeOH, 4d	110mg, 57%
1a	181 mg, 0.8 mmol	2:1	Open vessel, 14 mL non-degassed MeOH, 12d	104mg, 54%
1a	181 mg, 0.8 mmol	2:1	Open vessel, 14 mL degassed MeOH, 12d	103mg, 53%
1b	186 mg, 0.8 mmol	--	Open vessel, 14 mL non-degassed MeOH, 12d	--
1b	186 mg, 0.8 mmol	20:1	Open vessel, 14 mL non-degassed MeOH, 12d	129mg, 65%
1b	186 mg, 0.8 mmol	2:1	Open vessel, 14 mL non-degassed MeOH, 12d	101mg, 51%
1b	186 mg, 0.8 mmol	2:1	Open vessel, 14 mL degassed MeOH, 12d	90 mg, 45%
1b	186 mg, 0.8 mmol	--	Sealed vessel, degassed 20mL MeOH, 15d	--
1c	235 mg, 0.8 mmol	--	Open vessel, non-degassed 20 mL MeOH, 8d	--
1c	235 mg, 0.8 mmol	2:1	Sealed vessel, degassed 20 mL MeOH, 8d then open vessel and store 1d	173mg, 70%
1c	235 mg, 0.8 mmol	2:1	Open vessel, degassed 12 mL MeOH, 3d	180mg, 73%
1c	235 mg, 0.8 mmol	2:1	Open vessel, non-degassed 20 mL MeOH, 2d	190mg, 77%
1c	235 mg, 0.8 mmol	2:1	Open vessel, non-degassed 20 mL MeOH, 8d	200mg, 81%
1c	235 mg, 0.8 mmol	20:1	Sealed vessel, degassed 20 mL MeOH, 8d then open vessel and store 7d	174mg, 70%

SUP-4: Analytical data for **2a**, 3-phenyl-4H-benzo[e]-1,2,4thiadiazine-S-oxide

mp 218 °C (from MeOH);* **Elemental Analysis** calc. for C₁₃H₁₀N₂OS: C = 64.4%, H = 4.2%, N = 11.6%, found C = 63.8%, H = 4.3%, N = 11.4%; **IR** (solid, selected $\nu_{\max}/\text{cm}^{-1}$): 3200 (N-H), 1600 (C=N), (S=O) 999 m. **HRMS** ES(I) m/z [M + H]⁺ calc. for C₁₃H₁₁N₂OS: 243.0592, found 243.0591. **¹H NMR** (500 MHz, *d*⁶-DMSO) δ_{H} = 12.07 (1H, bs), 8.07 (2H, d, J = 7.5 Hz), 7.80 (1H, d, J = 7.0 Hz), 7.72 – 7.66 (2H, m), 7.65 – 7.60 (3H, m), 7.48 (1H, t, J = 7.5 Hz) ppm.

* This compound has been reported previously; Kresze *et al.* reported¹ **2a** as crystallising as colourless needles with a higher melting point (250 – 252 °C from EtOH) whereas Zienkiewicz *et al.* reported² melting to occur at 178 °C (dec.) for samples crystallised from CH₂Cl₂. The current sample crystallised as colourless lathes (mp 218 °C) indicating some potential for polymorphism in this system.

[1] G. Kresze, C. Seyfried and A. Trede, *Liebigs. Ann. Chem.* 1968, **715**, 223 – 237.

[2] J. Zienkiewicz, P. Kaszynski and V.G. Young Jr., *J.Org.Chem.*, 2004, **69**, 7525 – 7536.

SUP-5: Analytical data for **2b**, (3-thiophen-2-yl)-4H-benzo[e]-1,2,4-thiadiazine-S-oxide

mp 238 °C (from MeOH). **Elemental Analysis** calc. for C₁₁H₈N₂OS₂: C = 53.2%, H = 3.3%, N = 11.3%, found C = 53.1%, H = 3.2%, N = 11.2%. **IR** (solid, selected $\nu_{\max}/\text{cm}^{-1}$): 3234 (N-H), 1586 (C=N), 999 (S=O). **HRMS** ES(I) m/z [M + H]⁺ calc. for C₁₁H₉N₂OS₂: 249.0156, found 249.0159. **¹H NMR** (500 MHz, CDCl₃) δ_{H} = 11.77 (1H, bs), 7.53-7.51 (2H, m), 7.40 (1H, dd, J = 5.0, 1.0 Hz), 7.11 (1H, ddd, J = 7.60, 7.60, 1.4 Hz), 7.05 (1H, ddd, J = 7.5, 7.5, 1.0 Hz), 7.01 (1H, d, 8.1 Hz), 6.96 (1H, dd, J = 4.85, 3.95 Hz,) ppm.

SUP-6: Analytical data for **2c**, 6-(trifluoromethyl)-3-phenyl-4H-benzo[e]-1,2,4-thiadiazine-S-oxide

mp 241.5 °C (from MeOH). **Elemental Analysis** calc. for C₁₄H₉F₃N₂OS: C = 54.2%, H = 2.9%, N = 9.0%, found C = 54.2%, H = 3.0%, N = 9.0%. **IR** (solid, selected $\nu_{\max}/\text{cm}^{-1}$): 3230 (N-H), 1601 (C=N), 1019 (S=O). **HRMS** ES(I) m/z [M + H]⁺ calc. for C₁₄H₁₀F₃N₂OS: 311.0466, found 311.0464. **¹H NMR** (500 MHz, CDCl₃) δ_{H} = 11.84 (1H, bs), 7.69 (2H, d, 7.2 Hz), 7.63 (1H, d, 7.7 Hz), 7.49 (1H, dd, J = 7.5, 7.5 Hz), 7.37 – 7.27 (4H, m).

SUP-7: Crystallographic data for **4**, **2a**, **2b** and **2c**.

Data for complex **4** were measured on a Nonius-Kappa CCD area detector at 200(2) K using Mo-K α radiation ($\lambda = 0.71073 \text{ \AA}$) using ϕ and ω scans using the COLLECT software.[1] The cell was refined with HKL Scalepack and data reduced using HKL Denzo and Scalepack [2] and an absorption correction applied using SORTAV [3]. The structure was solved using SIR-92 [4] and refined against F^2 using SHELXL-97.[5] Data for compounds **2a** – **2c** were collected on a Bruker APEX-II CCD at 150(2) K using Mo-K α radiation ($\lambda = 0.71073 \text{ \AA}$) using ϕ and ω scans using the Bruker APEX-2 software [6]. The cell was refined and the data reduced using SAINT [6] and an absorption correction applied using SADABS [7]. The structures of **2a** – **2c** were solved using direct methods with SHELXS-97 [8] and refined against F^2 with SHELXL-97.[5] CCDC deposit numbers: 1027456-1027459.

- [1] COLLECT. Nonius BV, Delft, The Netherlands.
- [2] DENZO and SCALEPACK: Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, Macromolecular Crystallography, Part A, edited by C. W. Carter Jr & R. M. Sweet, pp. 307-326. New York: Academic Press.
- [3] R.H. Blessing, *Acta Cryst.*, 1995, **A51**, 33–38.
- [4] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M.C. Burla, G. Polidori and M. Camalli, *J. Appl. Cryst.*, 1194, **27**, 435
- [5] SHELXL-97, G.M. Sheldrick, *Acta. Cryst.*, 2008, **A64**, 112-122.
- [6] SAINT, Bruker AXS Inc., Madison, Wisconsin, USA
- [7] SADABS, Bruker AXS Inc., Madison, Wisconsin, USA.
- [8] SHELXS, G.M. Sheldrick, *Acta. Cryst.*, 2008, **A64**, 112-122.

Compound	4·MeOH	2a	2b	2c
Chemical formula	C ₄₈ H ₃₂ Cu ₂ N ₁₂ O ₄ S ₄ ·2 (CH ₄ O)	C ₁₃ H ₁₀ N ₂ OS	C ₁₁ H ₈ N ₂ OS ₂	C ₁₄ H ₉ F ₃ N ₂ OS
Formula weight	1160.32	242.29	248.31	310.29
T/K	200(2)	150(2)	150(2)	150(2)
Crystal size (mm)	0.25 × 0.15 × 0.05	0.45 × 0.20 × 0.17	0.41 × 0.20 × 0.18	0.31 × 0.17 × 0.06
Crystal habit	Green Rod	Colourless lathe	Colourless block	Pale yellow plate
Crystal System	Triclinic	Orthorhombic	Monoclinic	Monoclinic
Space group	<i>P</i> -1	<i>Pbca</i>	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁ / <i>c</i>
<i>a</i> (Å)	8.9974(18)	8.4577(5)	8.2057(5)	12.7488(9)
<i>b</i> (Å)	10.434(2)	11.9926(7)	18.0582(12)	8.6205(6)
<i>c</i> (Å)	14.204(3)	21.3438(13)	7.4221(4)	12.1309(8)
α (deg)	75.65(3)	90	90	90
β (deg)	88.65(3)	90	111.185(3)	101.918(3)
γ (deg)	68.44(3)	90	90	90
<i>V</i> (Å ³)	1198.1(5)	2164.9(2)	1025.48(11)	1304.46(16)
<i>Z</i>	1	8	4	4
D _{calcd} (g cm ⁻³)	1.608	1.487	1.608	1.580
μ (mm ⁻¹)	1.128	0.281	0.494	0.284
θ range (deg)	1.02 – 27.48	3.07 – 33.24	2.66 – 30.62	2.87 – 30.71
Reflns collected	11353	10187	8216	19374
Unique reflns	3124	1904	1808	2303
R _{int}	0.044	0.032	0.028	0.029
Data/restraints/parameters	3124/336/0	1904/185/0	1808/149/1	2303/190/0
R ₁ (<i>I</i> > 2σ(<i>I</i>)), wR ₂ (all data)	0.042, 0.111	0.044, 0.112	0.040, 0.095	0.035, 0.087
Residual electron density (e/Å ³)	+0.58/-0.50	+0.28/-0.38	+0.39/-0.33	+0.27/-0.22

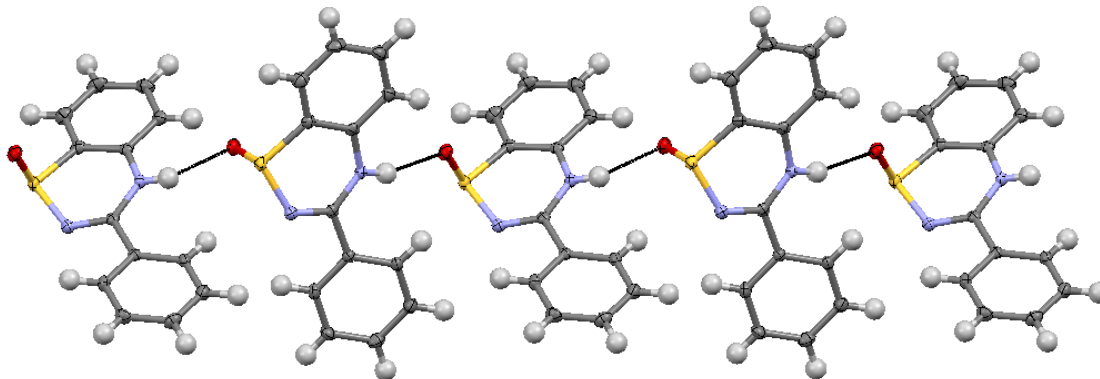
SUP-8: A comparison of bond lengths (Å) in the benzothiadiazines **1a** - **1c** with the corresponding benzothiadiazine S-oxides **2a** - **2c**.

Compound	1a	2a	1b	2b	1c*	2c
SO		1.504(2)		1.508(2)		1.498(1)
SN	1.720(1)	1.661(2)	1.713(2)	1.663(2)	1.71(1)-1.73(1)	1.663(2)
NC	1.293(2)	1.311(3)	1.299(2)	1.318(3)	1.29(1)-1.30(1)	1.312(2)
CN	1.378(2)	1.350(3)	1.368(2)	1.351(3)	1.37(1)	1.352(2)
NC	1.416(2)	1.398(3)	1.417(2)	1.393(3)	1.41(2)-1.43(2)	1.389(2)
CC	1.392(2)	1.393(3)	1.392(2)	1.392(4)	1.39(2)-1.41(1)	1.393(3)
CS	1.758(2)	1.771(2)	1.752(2)	1.768(3)	1.74(1)- 1.75(1)	1.772(2)

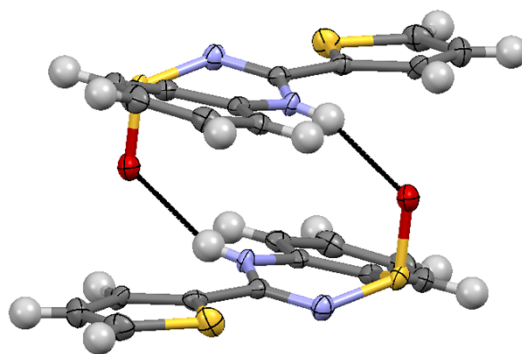
* Poor quality structure and with four molecules in the asymmetric unit.

SUP-9: Hydrogen-bonding N-H...O=S motifs in **2a** – **2c**.

Compound **2a**. Polymeric chain parallel to crystallographic *b*-axis. O...H 2.08(2) Å, N-H...O = 161(2)°



Compound **2b**. Centrosymmetric dimer. O...H 2.03(2) Å, N-H...O = 155(2)°



Compound **2c**. Polymeric chain parallel to crystallographic *c*-axis. O...H 2.02 Å, N-H...O = 157°

