

Mechanistic Insights into a Copper-Disulfide Interaction in Oxidation of Imines by Disulfides

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Supporting Information

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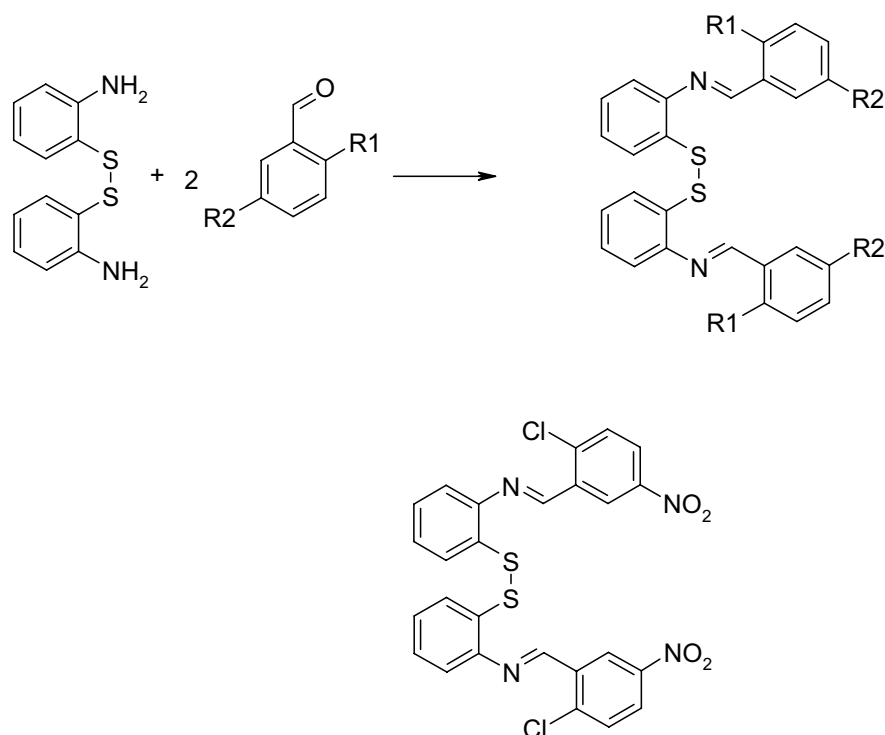
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General Experimental.

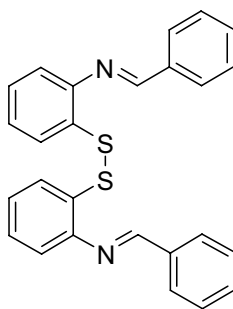
^1H NMR and ^{13}C NMR spectra were recorded on at 400 MHz NMR spectrometer. Chemical shifts are reported in δ ppm referenced to solvent residual peak (CDCl_3 : $^1\text{H} = 7.24$ ppm, $^{13}\text{C} = 77.23$ ppm) as the internal reference unless otherwise noted. Data are reported in the following order: chemical shifts are given (δ); multiplicities are indicated br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), app (apparent); coupling constants, J , are reported in Hz. Peaks in IR are reported in cm^{-1} . Melting points were determined on a Boetius block and were not corrected. Column chromatography procedures were followed using 70-230 mash and 60 Å silica gel. Visualization was effected with ultraviolet light.

DMA and THF were dried over 4Å molecular sieves and titrated with a Karl Fischer Coulometer (water content below 10 ppm) and purged with dry argon before using.

Preparation of the imine disulfides (Compounds 1a-b):



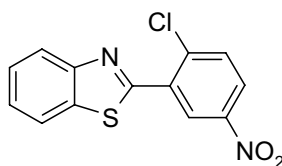
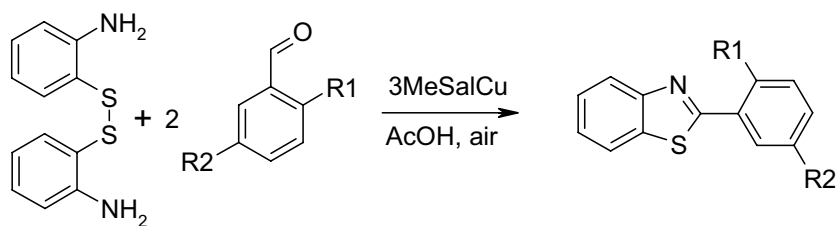
2,2'-disulfanediybis(*N*-(2-chloro-5-nitrobenzylidene)aniline)(1a): 2,2'-dithiodianiline (621 mg; 2.5 mmol) and 2-chloro-5-nitrobenzaldehyde (928 mg; 5 mmol) were dissolved in acetic acid (15 mL). The reaction mixture was stirred and heated at 80 °C for 2 h. Then reaction mixture was poured into the water and yellow precipitate was collected on frit and several times was washed by distilled water. After drying, the product was obtained as a yellow solid in 90 % yield (1.3061 g). The product was crystallized from CHCl₃ : hexane. M.p. 196-201 °C, ¹H NMR (400 MHz, CDCl₃) δ 9.15 (d, *J* = 2.8, 1H), 8.91 (s, 1H), 8.24 (dd, *J* = 2.8, 8.8, 1H), 7.75 – 7.69 (m, 1H), 7.61 (d, *J* = 8.8, 1H), 7.27 – 7.19 (m, 2H), 7.12 – 7.05 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 154.10, 148.12, 147.15, 141.79, 134.41, 132.79, 131.10, 128.12, 127.34, 127.05, 126.18, 124.14, 117.46, 77.31, 76.99, 76.68. IR (solid): 2360, 1608, 1574, 1525, 1466, 1346, 1245, 1052, 1037, 820, 759, 738 cm⁻¹. Anal. calcd for C₂₆H₁₆Cl₂N₄O₄S₂: C, 53.52; H, 2.76; N, 9.60. Found: C, 52.97; H, 2.82; N 9.22.



2,2'-disulfanediybis(*N*-benzylideneaniline)(1b): 2,2'-dithiodianiline (2.98 g; 12 mmol) and benzaldehyde (2.4 mL; 24 mmol) were dissolved in toluene (50 mL). Apparatus was equipped by extender with activated 4Å molecular sieves. The reaction mixture was stirred and heated to reflux for 1 h. Then toluene was evaporated and 98 % ethanol (about 10 mL) was added to the oily residue. The solution was stirred, heated and the product started to crystallize from the solution. The crystalline product was collected on frit, washed with hexane and recrystallized from ethanol. After drying, the product was obtained as yellowish crystals in 71% yield (3.55 g). M.p. 140-141 °C, (lit. 138.5-139.5 °C)¹. ¹H NMR (400 MHz, CDCl₃): δ 8.48 (s, 1H), 8.02 – 7.94 (m, 2H), 7.65 (dd, *J* = 1.5, 7.7, 1H), 7.54 – 7.44 (m, 3H), 7.22 – 7.11 (m, 2H), 7.04 (dd, *J* = 1.4, 7.6, 1H).

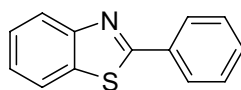
¹. Bogert, M. T.; Naiman B.; *J. Am. Chem. Soc.* **1935**, *57* (9), 1529-1533.

Preparation of the 2-phenylbenzo[d]thiazoles (Compounds 2a-b):



2-(2-chloro-5-nitrophenyl)benzo[d]thiazole (2a): 2,2'-Dithiodianiline (124.2 mg; 0.5 mmol), 2-chloro-5-nitrobenzaldehyde (185.6 mg; 1 mmol) and copper(I) 3-methylsalicylate (5.4 mg; 0.025 mmol; 5 %) were suspended in acetic acid (2 mL). The reaction mixture was stirred and heated at 80 °C for 3 h. Then the reaction mixture was poured into water and the precipitate was collected on frit. pH of the filtrate was adjusted to 9 by a solution of K₂CO₃. The filtrate was then extracted by dichloromethane (2x25 mL), the organic layers were combined, dried over MgSO₄, filtrated and evaporated. The residue after evaporation and the precipitate were combined and the crude product was purified by column chromatography (silica gel 15 g; dichloromethane: hexane: methanol 1:1:0.01). The product was obtained as a yellowish product in 78 % yield (226.1 mg). The product was crystallized from dichloromethane : hexane. M.p. 188-190 °C, (lit. 190-193 °C)². ¹H NMR (400 MHz, CDCl₃) δ 9.20 (d, J = 2.8, 1H), 8.23 (dd, J = 2.8, 8.8, 1H), 8.19 – 8.13 (m, 1H), 7.97 (ddd, J = 0.6, 1.1, 8.0, 1H), 7.70 (d, J = 8.8, 1H), 7.57 (ddd, J = 1.3, 7.2, 8.3, 1H), 7.47 (ddd, J = 1.2, 7.2, 8.2, 1H).

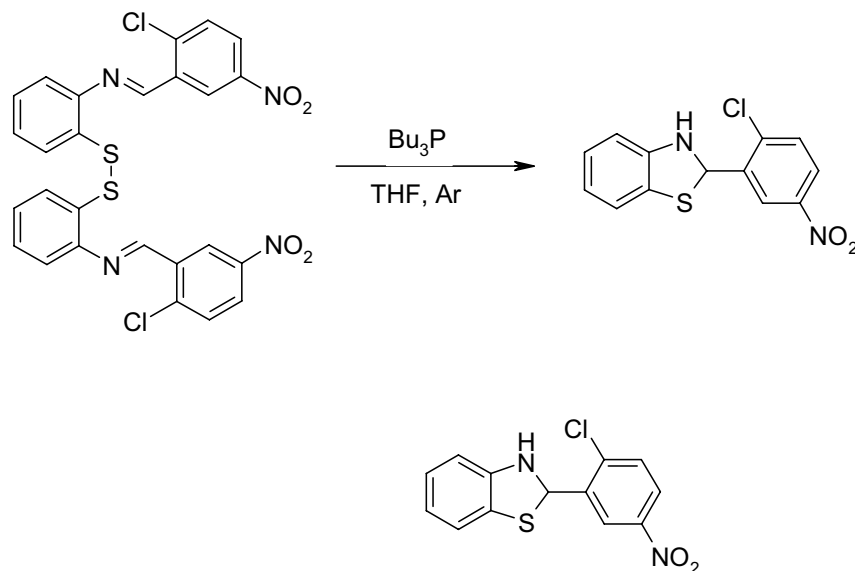
². Choi, S.-J.; Park, H. J.; Lee, S. K.; Kim, S. W.; Han, G.; Choo, H.-Y. P.; *Bioorg. Med. Chem.* **2006**, *14*, 1229-1235.



2-Phenylbenzo[d]thiazole (2b): 2,2'-Dithiodianiline (124.2 mg; 0.5 mmol), benzaldehyde (106.1 mg; 1 mmol) and copper (I) 3-methylsalicylate (5.4 mg; 0.025 mmol; 5 %) were dissolved in acetic acid (2 mL). The reaction mixture was stirred and heated at 80 °C for 4.5 h. Then the reaction mixture was poured into water and the precipitate was collected on frit. pH of the filtrate was adjusted to 9 by a solution of K₂CO₃. Then the filtrate was extracted by dichloromethane (2x25 mL), the organic layers were combined, dried over MgSO₄, filtered and evaporated. The residue after evaporation and the precipitate were combined and the crude product was purified by column chromatography (silica gel 10 g; dichloromethane: hexane : methanole 1:1:0.01). The product was obtained as a white solid in 74 % yield (156.6 mg). The product was crystallized from hexane. M.p. 110-112 °C, (lit. 110.5-111 °C)³. ¹H NMR (400 MHz, CDCl₃): δ 8.13 – 8.03 (m, 3H), 7.89 (ddd, J = 0.6, 1.2, 8.0, 1H), 7.53 – 7.44 (m, 4H), 7.37 (ddd, J = 1.2, 7.3, 8.3, 1H).

³. Inamoto, K.; Hasegawa, C.; Hiroya, K.; Doi, T.; *Org. Lett.* **2008**, *10* (22), 5147-5150.

Preparation of 2-(2-chloro-5-nitrophenyl)-2,3-dihydrobenzo[*d*]thiazole (Compound 3a):



2-(2-Chloro-5-nitrophenyl)-2,3-dihydrobenzo[*d*]thiazole (3a): 2,2'-Disulfanediylbis (*N*-(2-chloro-5-nitrobenzylidene)aniline) (1a) (682 mg; 1.1688 mmol) was dissolved in THF (4.7 mL) under argon. 5% HCl (0.5 mL) was added to the solution. The suspension was stirred at room temperature and tributylphosphine (111.3 mg; 136 μL) was added dropwise. After 20 minutes, the reaction mixture was poured into water and the precipitate was collected on frit. The crude product was crystallized from dichloromethane: hexane mixture. After drying, the product was obtained as orange crystals in 72 % yield (495 mg). M.p. 135-138 $^\circ\text{C}$. ^1H NMR (400 MHz, CDCl_3) δ 8.57 (d, $J = 2.7$, 1H), 8.07 (dd, $J = 2.7, 8.7$, 1H), 7.53 (d, $J = 8.7$, 1H), 7.07 – 6.97 (m, 2H), 6.90 – 6.85 (m, 1H), 6.82 (td, $J = 1.1, 7.5$, 1H), 6.59 (s, 1H), 4.53 (s, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 147.23, 145.63, 142.80, 138.46, 130.83, 126.51, 126.15, 124.03, 122.85, 122.32, 122.15, 112.01, 65.00. IR (solid): 1609, 1577, 1528, 1472, 1402, 1349, 1263, 1242, 1192, 1099, 1040, 928, 832, 783, 747, 738, 726, 667, 644, 529 cm^{-1} . Anal. calcd for $\text{C}_{13}\text{H}_9\text{ClN}_2\text{O}_2\text{S}$: C, 53.34; H, 3.10; N, 9.57. Found: C, 53.16; H, 2.96; N 9.37.

Experiment with catalytic copper under argon

2,2'-Disulfanediyl bis (*N*-(2-chloro-5-nitrobenzylidene)aniline) (**1a**) (145.9 mg; 0.25 mmol), copper(I) 3-methylsalicylate (2.7 mg; 0.0126 mmol; 5 %) and internal standard naphthalene (32.1 mg, 0.25 mmol) were suspended in degassed acetic acid (2 mL). The reaction mixture was stirred and heated at 80 °C for 3 h. In order to obtain the most accurate results the analysis was based on multiple samples. Hence, six samples of the reaction mixture were sequentially diluted by 5 % HCl and extracted by ethyl-acetate. Organic layers were analyzed by UPLC. (**Table 1**).

Table 1: yield of product **2a** and **3a**

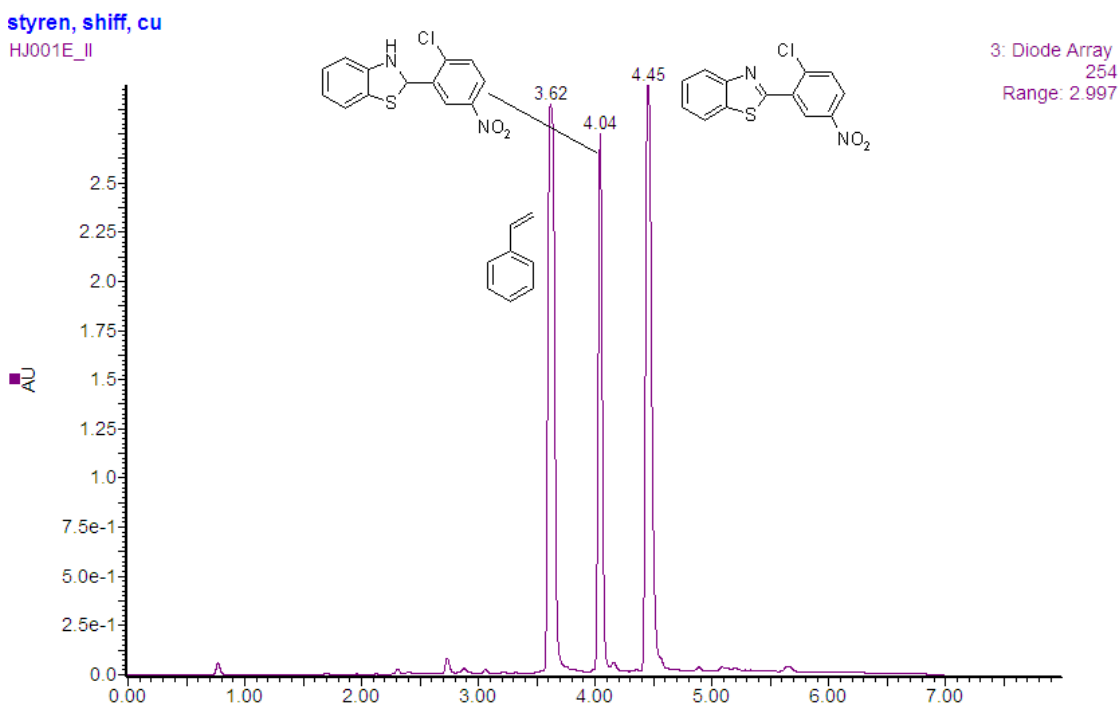
sample	area 2a to std (%)	yield of 2a (%)	area 3a to std (%)	yield of 3a to std (%)
a	50	38	43	34
b	47	31	39	22
c	44	24	38	20
d	42	21	41	26
e	45	26	42	31
f	46	27	40	25

Values of concentrations **2a** and **3a** were found (28 ± 6) and (27 ± 6) % respectively.

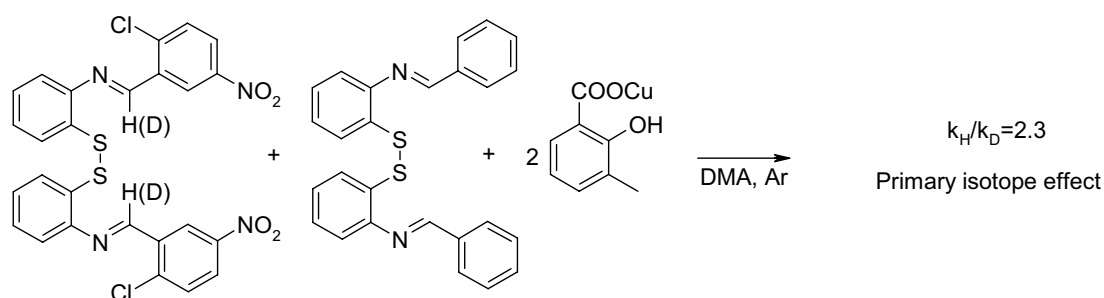
Experiment with external nucleophile (styrene)

2,2'-Disulfanediyl bis (*N*-(2-chloro-5-nitrobenzylidene)aniline) (**1a**) (116.3 mg; 0.20 mmol), styrene (57.3 mg; 0.55 mmol) and copper(I) 3-methylsalicylate (4.3 mg; 0.02 mmol; 10 %) were suspended in degassed acetic acid (1 mL) under argon. The reaction mixture was stirred and heated at 80 °C for 3 h. Sample of reaction mixture was analyzed by UPLC (**Picture 1**).

Picture 1: Chromatogram of reaction mixture

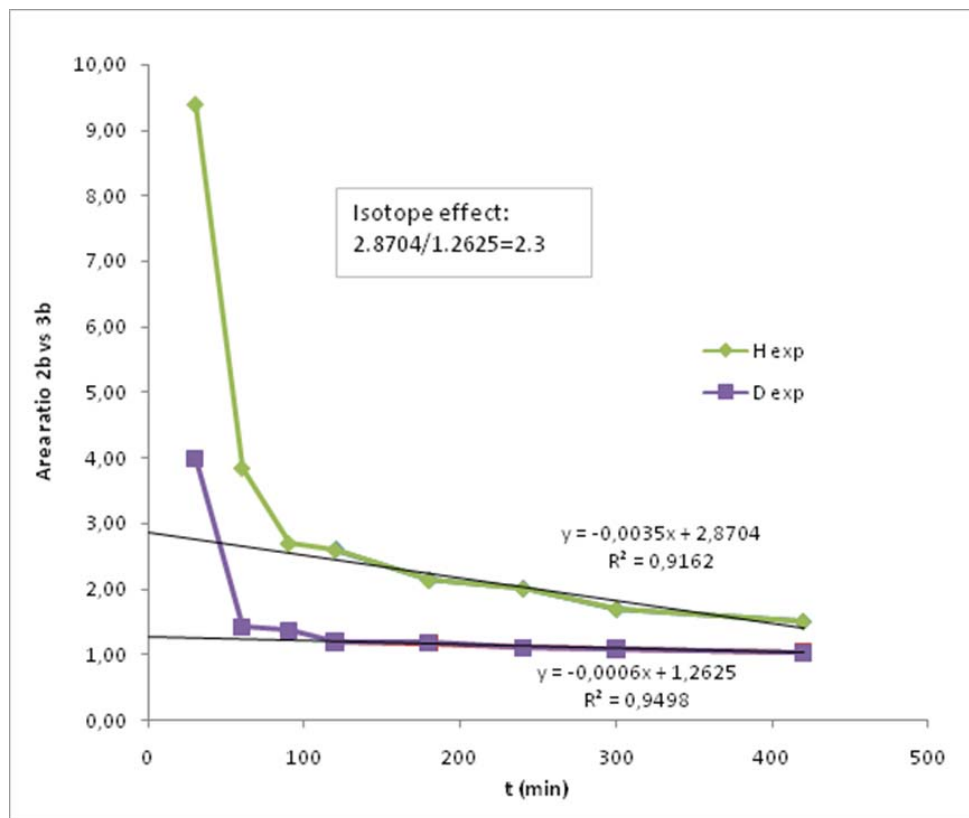


Kinetic Isotope Experiments – [1+2] competition

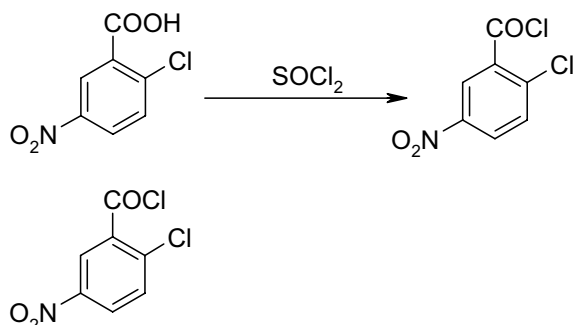


2,2'-Disulfanediyldis (*N*-(2-chloro-5-nitrobenzylidene)aniline) (**1a**) (5.1 mg; 0.0087 mmol), 2,2'-disulfanediyldis(*N*-benzylideneaniline) (**1b**) (3.7 mg; 0.0087 mmol), internal standard (naphthalene) (1.1 mg; 8.6 mg) and copper(I) 3-methylsalicylate (3.7 mg; 0.0172 mmol; 200 %) were dissolved in dry and degassed DMA (2.5 mL) under argon. The reaction mixture was stirred and heated at 80 °C. Samples of the reaction mixture were analyzed by UPLC. The results from the two independent experiments were reported and their median value was used for further calculation. The value of isotope effect, interpolated to $t = 0$ min, was thus established as 2.3 (**Picture 2**).

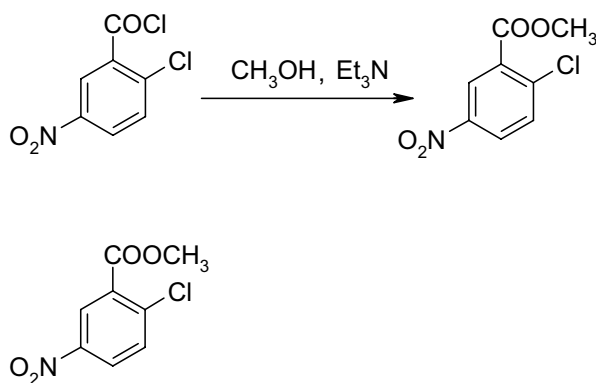
Picture 2: Isotope effect



Preparation of α,α' -dideuterio-2,2'-disulfanediyldis(*N*-(2-chloro-5-nitrobenzylidene) aniline)



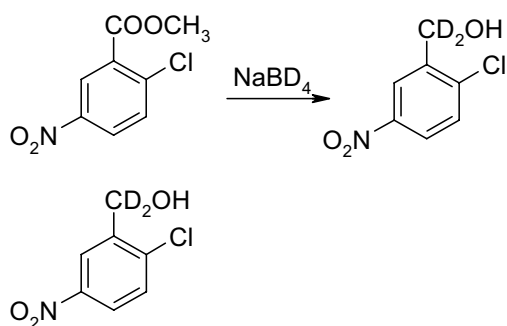
2-Chloro-5-nitrobenzoyl chloride (4a): A mixture of 2-chloro-5-nitrobenzoic acid (20.2 g; 100 mmol) and SOCl_2 (36 mL; 500 mmol) was heated for 8 h at 70 °C. SOCl_2 was evaporated and residue after evaporation was dissolved in a small amount of dichloromethane. Hexane was added and the mixture was allowed to stand for 8 h at 0 °C. The product was filtered and washed with small amount of cold hexane. After drying, the product was obtained as white crystals in 92 % yield (20.3 g). M.p. 56-58 °C, (lit. 60 °C)⁴. ¹H NMR (400 MHz, CDCl_3) δ 8.90 (d, $J = 2.6$, 1H), 8.36 (dd, $J = 2.6, 8.8$, 1H), 7.71 (d, $J = 8.8$, 1H).



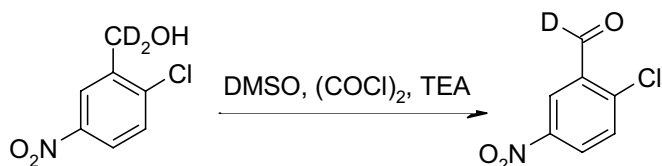
Methyl 2-chloro-5-nitrobenzoate (4b): Triethylamine (3.0 mL; 22 mmol) was added into the methanol (10 mL). Solution was cooled to 0 °C and 2-chloro-5-nitrobenzoyl chloride (4a) (3.32 g; 15 mmol) was added in several portions. Then cooling bath was removed and the reaction mixture was stirred for 5 minutes. The reaction mixture was

⁴ Cohen, J.B.; Armes, H.P.; *J. Chem. Soc., Trans.* **1906**, 89, 458.

slowly poured into cold water and stirred for 10 minutes and resulting precipitate was collected on frit. After drying, the product was obtained as a white solid in 94 % yield (3.06 g). M.p. 68-69 °C, (lit. 69-70 °C)⁵. ¹H NMR (400 MHz, CDCl₃) δ 8.69 (d, J = 2.7, 1H), 8.25 (dd, J = 2.8, 8.8, 1H), 7.63 (d, J = 8.8, 1H), 3.97 (s, 3H).

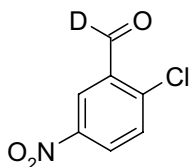


2-Chloro- α,α' -dideuterio-5-nitrobenzyl alcohol (4c): Sodium borodeuteride (217 mg; 5.2 mmol) was suspended in THF (6 mL) and the suspension was cooled to 0 °C. Ethanol was slowly added to the stirred suspension and solution of methyl 2-chloro-5-nitrobenzoate (4b) (1.00 g; 4.64 mmol) in THF was added dropwise. The cooling bath was removed and reaction mixture was allowed to warm to a room temperature. The reaction mixture was heated to 80 °C for 3 h. The reaction mixture was then poured into water and stirred overnight. Resulting suspension was extracted by dichloromethane (3x25 mL), washed by brine, dried over MgSO₄, filtered and evaporated. The crude product was purified by column chromatography (silica gel 12 g; hexane:diethylether:acetone 7:1:2). After evaporation and drying, the product was obtained as yellowish crystals in 69 % yield (611 mg). M.p. 71-73 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.44 (d, J = 2.7, 1H), 8.09 (dd, J = 2.7, 8.7, 1H), 7.50 (d, J = 8.7, 1H)⁶.

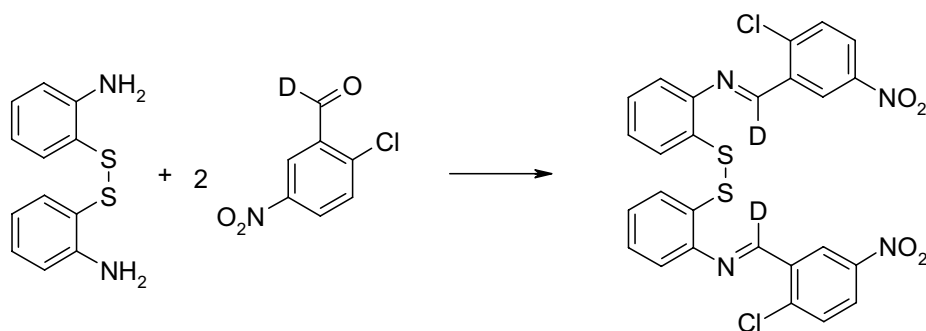


⁵ Chandler, W. D.; Bergman, J. J.; Haas, G. H.; *Can. J. Chem.* **1971**, *49*, 583-587.

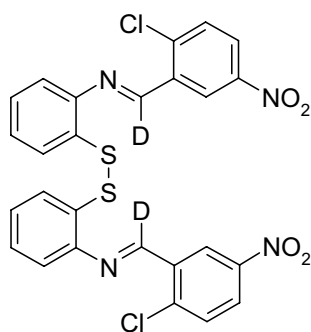
⁶ Gill, A.-L. at all; *J. Med. Chem.* **2005**, *48*(2), 414-426.



2-Chloro-5-nitrobenzaldehyde- α -d₁ (4d): Oxalyl chloride (330 μ L; 3.90 mmol) was dissolved in dichloromethane under argon. The solution was cooled to -60 °C and dimethyl sulfoxide (600 μ L; 8.44 mmol) dissolved in dichloromethane was added over 5 minutes. After 10 minutes, solution of 2-Chloro- α,α' -dideuterio-5-nitrobenzyl alcohol (4c) (556 mg; 2.93 mmol) in dichloromethane was added during 5 minutes. The reaction mixture was stirred for 15 minutes and triethylamine (2.4 mL; 17.22 mmol) was added in 5 minutes with stirring at -60 °C. The cooling bath was removed and water was added at room temperature. Stirring was continued for another 10 minutes and organic layer was separated. The aqueous phase was re-extracted with dichloromethane, and the organic layers were combined, washed with brine and dried over MgSO₄, filtered and evaporated. The crude product was purified by column chromatography (silica gel 33 g; hexane: diethylether:acetone 7:1:2). After evaporation and drying, the product was obtained as yellowish crystals in 49 % yield (266 mg). The product was recrystallized from hexane. M.p. 74-76 °C.. ¹H NMR (400 MHz, CDCl₃) δ 8.75 (d, J = 2.8, 1H), 8.37 (dd, J = 2.8, 8.8, 1H), 7.67 (d, J = 8.8, 1H)⁷.



⁷. AIST database



α,α' -Dideuterio-2,2'-disulfaneylbis(*N*-(2-chloro-5-nitrobenzylidene) aniline) (4e): 2,2'-dithiodianiline (73.2 mg; 0.295 mmol) and 2-chloro-5-nitrobenzaldehyde- α -d₁ (4d) (109.6 mg; 0.587 mmol) were dissolved in acetic acid (5 mL). The reaction mixture was stirred and heated at 80 °C for 1 h. The reaction mixture was then poured into water and a yellow precipitate was collected on frit and washed several times by distilled water. After drying, the product was obtained as a yellow solid in 93 % yield (160.0 mg). The product was crystallized from dichloromethane : hexane. M.p. 196-202 °C, ¹H NMR (400 MHz, CDCl₃) δ 9.15 (d, J = 2.7, 1H), 8.24 (dd, J = 2.7, 8.8, 1H), 7.76 – 7.69 (m, 1H), 7.61 (d, J = 8.8, 1H), 7.30 – 7.18 (m, 2H), 7.11 – 7.05 (m, 1H). (see **1a**).

Experimental details.

The mass spectrometric experiments were performed with a Finnigan LCQ Classic ion-trap mass spectrometer as described elsewhere.⁸ The investigated ions were generated by electrospray ionization (ESI) of equimolar solutions of copper(I) 3-methylsalicylate and the desired disulfides in pure methanol. The solutions were infused into the ESI source using a syringe pump at a flow rate of 5 $\mu\text{L}\cdot\text{min}^{-1}$ applying a spray voltage of 4.5 kV, nitrogen as a sheath gas, and the transfer capillary kept at 200 °C. The ions produced via ESI are then transferred to a Paul ion-trap for ion storage and manipulation⁹ in the presence of ca. 10^{-5} mbar helium as a trapping gas. For detection, the ions are ejected from the trap to an electron multiplier. Low-energy collision-induced dissociation (CID) was performed by application of an excitation AC voltage to the end caps of the trap to induce collisions of the isolated anions with the helium buffer gas for a period of 20 ms. Conversion of the excitation amplitudes to approximate collision energies was achieved by calibration of the fragmentation thresholds to that of the well-known $[(\text{pyridine})_2\text{Cu}]^+$ cation.^{10,11} The Xcalibur software version 1.3 was used for instrument control, data acquisition and data processing.

⁸. Tintaru, A.; Roithová, J.; Schröder, D.; Charles, L.; Jušinski, I.; Glasovac, Z.; Eckert-Maksić, M.; *J. Phys. Chem. A* **2008**, *112*, 12097-12103.

⁹. R. A. J. O'Hair *Chem. Commun.* **2006**, 1469-1481.

¹⁰. Than, S.; Maeda, H.; Irie, M.; Itoh, S.; Kikukawa, K.; Mishima, M. *J. Phys. Chem. A* **2007**, *111*, 5988-5994.

¹¹. Révész, Á.; Sztáray, B.; Milko, P.; Roithová, J.; Schröder, D., in preparation.

