Electrochemical Synthesis of Imidazolyl Disulfides

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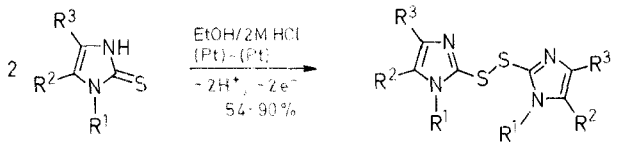
Imidazole-2(3*H*)-thione (**1a**), 4,5-diphenylimidazole-2(3*H*)-thione (**1b**), 1-methylimidazole-2(3*H*)-thione (**1c**, mercaptazole, mercazolyl, methimazole), benzimidazole-2(3*H*)-thione (**1d**) and 5-methylbenzimidazole-2(3*H*)-thione (**1e**) are electrochemically oxidized to the corresponding disulfides **2a–e**, respectively.

Although there are many procedures for converting thiols to disulfides, there is no general method for oxidizing imidazole-2(3*H*)-thiones **1** to imidazolyl disulfides **2**.[1-11] The disulfides of imidazole-2(3*H*)-thiones **1** are important reagents for the cyclization of long chain hydroxy acids to macrocyclic lactones[11] and useful intermediates in the manufacture of pharmaceuticals.[1] The synthesis of *N*-methylimidazolyl disulfide (**2c**) is also of interest since 1-methyl-2-imidazole-2(3*H*)-thione (mercaptazole, mercazolyl, methimazole, **1c**) has been implicated in the inhibition of the thyroid peroxidase-catalyzed iodination of thyroglobulin.[10-13]



1 **2**

1, 2	R^1	R^2	R^3
a	H	H	H
b	H	Ph	Ph
c	CH_3	H	H
d	H	$-(CH=CH)_2-$	
e	H	$-CH=C(CH_3)CH=CH-$	

Imidazole-2(3*H*)-thiones **1** react with diiodine, which converts many thiols and thiones to disulfides, to form 1:1 and 2:1 thione-diiodine charge-transfer complexes in nonaqueous solvents.[13-19] It is also of interest to note that although many compounds containing thiocarbonyl groups[20-31] (thioacids,[22,23] thioureas[24,25]) undergo electrodimerization to afford the disulfide linkage, other compounds (heterocyclic thiones) in this class eliminate sulfur to form a sulfide link[26,27,31] or react with water to yield the corresponding carbonyl compound.[28] A recent study[29] of the electrochemistry of 2-thioxanthine showed that oxidation of the purine ring precedes the oxidation of the thiol group. In this report, we describe a facile preparative electrodimerization procedure for the synthesis of imidazolyl disulfides **2** from imidazole-2(3*H*)-thiones **1** (Table 1).

Initial attempts to prepare disulfides **2** in 2 M aqueous hydrochloric acid were fraught with solubility problems. Thione **1b** was not sufficiently soluble in 2 M aqueous hydrochloric acid, and ethanenitrile was added to the thione **1c** reaction mixture to increase solubilization. However, dissolving 4,5-diphenylimidazole-2(3*H*)-thione (**1b**) in ethanol and thiones **1a**, **1c**, **1d**, and **1e** in 2 M ethanolic hydrochloric acid eliminated solubility problems and enhanced the yields of the disulfides **2** (Table). Substitution at carbon or nitrogen of the parent thione **1a** appears to improve the yield of disulfides **2**.

This facile electrochemical oxidation at controlled potential allows preparation of imidazolyl disulfides **2** from imidazole-2(3*H*)-thiones **1** without overoxidation, without use of hazardous chemicals (e.g. phosgene),[1] and without introduction of other substances into the system.

Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. Microanalyses were performed by Robertson Laboratory, Madison, New Jersey. Mass spectra were obtained on a Finnigan GC/EI-CI mass spectrometer with a Nova 3 Data system. ^{1}H- and ^{13}C-NMR spectra were obtained on Bruker WM-250 and General Electric FT QE-300 NMR spectrometers. The Bruker WM-250 spectrometer was controlled by a Bruker Aspect 2000 computer.

Thiones **1b–e** are commercially available.[32] Imidazole-2(3*H*)-thione (**1a**) was prepared as previously described.[33]

Table. Compounds **2** Prepared

Product	Yield (%)	mp (°C) found	mp (°C) reported	^{1}H-NMR (DMSO-d_6/TMS) δ, J(Hz)	^{13}C-NMR (DMSO-d_6/TMS)[a] δ	MS m/z (%)
2a	54	152–154 (dec)	155[1]	7.23 (s, 2H, 2 × =CHNH); 8.48 (s, 2H, 2 × =CHN=)	129.81 (C-4,5); 142.10 (C-2)	199 (MH^+, 15); 101 (100)
2b	72	222–225 (dec)	250[1]	7.33–7.42 (s, 2 × C_6H_5)	128.74 (C-4,5); 131.60, 132.10, 132.66 (C_{arom}); 142.80 (C-2)	503 (MH^+, 0.5); 253 (100)
2c	90	126–127	127–128[1,9]	3.42 (s, 6H, 2 × NCH_3); 7.04 (s, 2H, 2 × =CHNH); 7.34 (s, 2H, 2 × =CHN=)	35.74 (NCH_3); 128.45 (C-5); 132.89 (C-4); 140.37 (C-2)	227 (MH^+, 13); 115 (100)
2d	77	230–232 (dec)	230 (dec)[18]	7.61 (dd, 2H, J = 6.18, 2 × =CHN=); 7.93 (dd, 2H, J = 6.27, 2 × =CHNH); 10.64 (s, 2H, 2NH)	113.88[b]; 126.64[c]; 136.48 (C-2,4)	151 (100)
2e[e]	80	281–282 (dec)	281–283 (dec)[19]	2.35 (s, 3H, CH_3); 2.51 (s, 3H, CH_3); 6.95 (d, 1H_{olefin}, J = 8.07); 7.02 (s, 1H_{olefin}); 7.10 (d, 1H_{olefin}, J = 8.06); 7.42 (d, 1H_{olefin}, J = 8.49); 7.68 (s, 1H_{olefin}); 7.78 (d, 1H_{olefin}, J = 8.45)	25.13 (CH_3); 113.42[d]; 113.89[b]; 127.44[c]; 134.39 (C=CH_3); 135.91 (C-4); 136.65 (C-2)	165 (100)

[a] The central solvent (DMSO-d_6) resonance at δ = 43.50 was used as reference.
[b] Carbon atom *ortho* to heterocyclic ring.
[c] Carbon atom *meta* to heterocyclic ring.
[d] Carbon atom *ortho* to heterocyclic ring and *ortho* to CH_3.
[e] As a 58 : 42 mixture of isomers.

Imidazolyl Disulfides 2a, c–e; General Procedure:
The disulfides of imidazole-2(3*H*)-thiones **1a**, **1c**, **1d**, and **1e** are prepared by controlled potential electrolysis in ethanolic 2 M aqueous HCl solution (84 mL EtOH + 16 mL conc. HCl) using a three electrode system. The controlled potential electrolysis is performed under an argon atmosphere at 0.6 to 0.7 volt (usually = 0.10 volt above the thione oxidation potential) using a Princeton Applied Research Model 173 Potentiostat with Model 179 Digital Coulometer and Model 178 Probe. A three-electrode cell consisting of a calomel reference electrode, a platinum gauze electrode, and a platinum foil counter electrode is used. The counter electrode is placed in 2 M HCl in a glass tube sealed at one end with fritted disk. The other electrodes are in the sample solution. The thione (ca. 0.2 to 0.3 g, ca. 1.5 to 2.8 mmol) is dissolved in ethanolic 2 M HCl solution (100 mL) and electrolyzed at constant voltage until the current reached zero or became negligible. The solution turns yellow during electrolysis and becomes more intensely yellow on neutralization (to Litmus paper) with cold (ca. 5 °C) sat. $NaHCO_3$. The product is extracted with $CHCl_3$ (3×25 mL). The extracts are combined, dried (Na_2SO_4), filtered, and the solvent is removed on a rotary evaporator at 22–24 °C. The yellow residue is dried *in vacuo* and, when necessary, recrystallized from EtOAc.

4,5-Diphenylimidazolyl Disulfide (2b):
Thione **1b** is dissolved in EtOH (22–24 °C) and this solution is slowly added to the 2 M ethanolic HCl solution during electrolysis at 0.8 volt. The rate of addition of thione **1b** must be sufficiently slow to preclude precipitation during electrolysis. The product **2b** is isolated as described above.

Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the National Science Foundation (CHE 86-19651) for support of this research. NMR and mass spectra were determined at University of California, Irvine with spectrometers obtained with the assistance of the National Science Foundation instrumentation program.

Received: 5 August 1988; revised: 10 March 1989

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1989

– Freeman, F.; Keindl, M.C.; Po, H.N.; Brinkman, E.; Masse, J.A. *Synthesis* **1989**, 714. On page 714 the data for compounds **2d** and **2e** in the Table should be corrected as follows:
2d:
^{1}H-NMR (500 MHz, DMSO-d_6): δ = 7.213 (H-5), 7.225 (H-6), 7.547 (H-4), 7.558 (H-7); $J_{4,7}$ = 5.94 Hz, $J_{5,6}$ = 6.03 Hz, $J_{4,7}$ = 166.61 Hz, $J_{4,5}$ = 166.70 Hz.
^{13}C-NMR (500 MHz, DMSO-d_6): δ = 119.0 (br, C-7), 119.1 (br, C-4), 126.60 (C-5, C-6), 143.27 (C-3a, C-7a), 151.21 (C-2).
2e: mp 190–191 °C.

$C_{16}H_{14}N_4S_2.1.5H_2O$ (353.5)	calc.	C54.37	H4.85	N15.85	S18.14
	found	54.71	4.63	15.66	17.94

^{1}H-NMR (500 MHz, DMSO-d_6): δ = 2.39 (s, 3H, CH_3), 7.04 (d, 1H, J = 8.11 Hz, H-5), 7.34 (s, 1H, H-7), 7.43 (d, 1H, J = 8.11 Hz, H-4).
^{13}C-NMR (500 MHz, DMSO-d_6): δ = 25.24 (CH_3), 118.05 (v. br, C-4, C-7), 128.13 (C-5), 136.14 (C-6), 142.42 (v. br, C-3a, C-7a), 150.37 (br, C-2).
EIMS (70 eV): m/z = 326 (m^+, 9.8%), 164 (100%).
CIMS: m/z = 327 (MH^+, 7.9%), 165 (100%).

1990

– Lin, Z.-Y.; Shi, W.; Zhang, L. *Synthesis* **1990**, 235. On page 236 compound **4b** should be named 7-acetoxy-4,8-dioxo-5-oxatetracyclo[8.2.1.0^{2,9}.0^{3,7}]tridec-11-ene; and compound **5** should be named 4,8-dioxo-5-oxatetracyclo-[8.2.1.0^{2,9}.0^{3,7}]tridec-11-ene.

– Lee, C.; Field, L. *Synthesis* **1990**, 391. On page 392 column 2, line 19, the statement in parenthesis should read: (cf. **7**; see Scheme **B** for general equation). While Scheme **C** should be: R^1SO_2X + 4-MeC_6H_4SH (2 equiv) (conditions: 1. Et_3N (2 equiv)/CH_2CH_2, −76 °C; 2. conc HCl → R^1SO_2H
On page 393 in Scheme **D** the temperature of the reaction of **16** with **17** should be −76 °C.
On page 394–395 in Table 1, the yield of sulfinic acid **15g** should read: 80 (−)^{21}; the reference in footnote e should be Ref. 2 and not Ref. 22.
On page 396 in Table 2 for compound **10p** the molecular formula should be referenced to Ref. 10; the 1130 cm^{-1} absorption in its IR spectral data should be designated (s).
On page 397 the sentence should read: The structure of **21** (C, H anal ± 0.3%) is confirmed by heating ...

– Lajoie, G.; Crivici, A.; Adamson, J.G. *Synthesis* **1990**, 571. On page 572 in the Table, compounds **1** and **2** should be **3** and **4**, respectively.

– Legraverend, M.; Boumchita, H.; Bisagni, E. *Synthesis* **1990** 587.
On page 588, 2,5-diamino-4,6-dichloropyridine (**5**) should be replaced by 2,5-diamino-4,6-dichloropyrimidine (**5**).

– Tietze, L.F.; Wünsch, J.R. *Synthesis* **1990**, 985.
On page 989, in the general procedure of the photoklysis sodium hydrogen carbonate (1.1 mmol) should be used instead of sodium hydrogen sulfate.