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Synthesis of Disulfides *via* Sulfenylation of Alkyl and Aryldithiopyridine N-Oxides

Derek H. R. Barton[1]*, Chen Chen[1] and G. Michael Wall[2]

[1]Department of Chemistry, Texas A&M University, College Station, Texas 77843

[2]Alcon Laboratories, Inc., 6201 S. Freeway, Fort Worth, Texas 76134

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Abstract: *Alkyl and aryldithiopyridine N-oxides were prepared by the reaction of 2,2'-dithiopyridine-1,1'-dioxide with various thiols in high yields. Some of the mixed disulfide products could in turn be used to sulfenylate efficiently other thiols. Therefore, practical and efficient synthetic methods for both symmetrical and unsymmetrical disulfides were developed.*

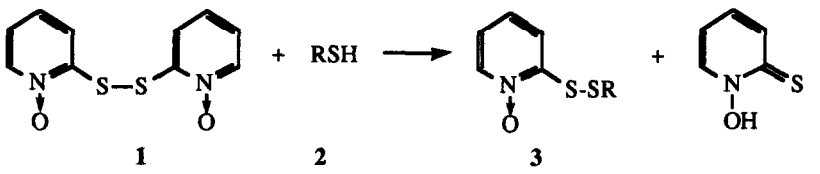
Ongoing research by our group has included investigations of the use of acyl derivatives of *N*-hydroxy-2-thiopyridone as convenient and powerful sources in radical reactions and syntheses[1]. One of these compounds being investigated by our group and others, N-acetoxypyridine 2-thione (also known as *methyl Barton ester*), was observed to degrade in an unusual manner when subjected to tungsten or ultraviolet irradiation in methanol to give 2-methylthiopyridine N-oxide and 2,2'-dithiodipyridine-1,1'-dioxide, **1**[2]. This and other observations led to investigations of reactions of pyridine N-oxide analogues, particularly compound **1**, with various thiols, finding that these compounds might be good general purpose sulfenylating agents. Attractive features included their efficiency, ease of preparation and handling.

The sulfenylation of thiols to prepare symmetrical and unsymmetrical disulfides has been an interesting project in organic chemistry[3]. Literature reports of sulfenylating agents other than sulfenyl chloride have included sulfenamides and sulfenimides[4,5]. Among them, N-alkyl or arylthiophthalimides proved to be good sulfenylating agents in most cases[5]. Other sulfenimide analogues have been investigated recently[6]. A disadvantage of these compounds was their preparation from sulfenyl halides[5a]. In the penicillin series, derivatives of azetidinone unsymmetrical disulfides were obtained by trapping thermally derived sulfenic acids (from the penicillin sulfoxides) with thiols[7,8]. Among the various general methods, the most promising involved the conversion of a thiol into a sulfenyl hydrazide using diethylazodicarboxylate, developed by Mukaiyama and Takahashi[9]. Hesse et al. have recently established a rather general procedure for the preparation of sulfenylating agents from thiols by conversion of the thiol into a latent sulfenylating agent, i.e., alkyl (or aryl) pyridyl disulfide which was then activated in a second step by alkylating the pyridine derivative[10]. The purpose of this study was to investigate general synthetic methods utilizing alkyl and aryldithiopyridine N-oxides to produce a variety of disulfides utilizing thiohydroxamic acid as a "good leaving moiety."

One agent chosen for its sulfenylating ability was the dimeric sulfide, 2,2'-dithiodipyridine-1,1'-dioxide, **1** (also known as Omadine® disulfide). Disulfide **1** has been prepared by the oxidation of 2-mercaptopyridine N-oxide (sodium Omadine®[11]) with hydrogen peroxide[12, 13]. It has also been identified as an oxidative[14] and

photolytic[15] decomposition product in solutions of 2-mercaptopyridine N-oxide. Its reactions with various thiols were investigated. Reactions of 2,2'-dithiodipyridine-1,1'-dioxide, **1**, with some thiols, **2**, gave a mixed disulfide, **3**, with the release of a stable thiohydroxamic acid as shown in Equation (1).

Equation 1



(1)

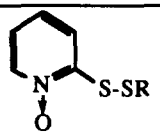
1 **2** **3**

Thiohydroxamic Acid
2a, 3a R = nC_3H_7
2b, 3b R = CH_2COOH
2c, 3c R = $CH_2CH(NHAc)COOH$
2d, 3d R = C_6H_5
2e, 3e R = $C_6H_5(2\text{-}OMe)$

This reaction was usually carried out in dichloromethane and/or chloroform at room temperature. The rate of this reaction varied greatly with the choice of thiol. For example, the reaction of disulfide, **1**, with 2-methoxythiophenol, **2e**, was complete in about one hour, while the reaction with n-propylthiol, **2a**, yielded mostly starting material after two days. The poor solubility of the disulfide, **1**, in solvents such as dichloromethane and chloroform was a serious problem with the "inactive" thiols. This problem was often solved with the incorporation of acetic acid as the solvent. For example, the reaction of disulfide, **1**, with N-acetyl-L-cysteine, **2c** (AcCys), in acetic acid afforded the expected disulfide, **3c**, in 83% yield. In some cases, the poor solubility of **1** was overcome by the greater solubility of the thiol in the reaction medium: addition of **1** to water produced an insoluble slurry which became clear upon the addition of N-acetyl-L-cysteine, resulting in a 64% yield[16] of disulfide **3c**. A more practical way to enhance solvation was to add a small amount of acetic acid to assist in dissolution of **1** in dichloromethane and chloroform. Thus, five unsymmetrical disulfides, **3**, were prepared in very high yields as summarized in Table 1. Satisfactory spectral (proton and carbon NMR, IR, MS) and microanalytical data were obtained. All of these disulfides were white crystals[17], very stable in air. Compounds **3a**, **3d**, and **3e** were freely soluble in chloroform: 3b and 3c could be dissolved in aqueous sodium bicarbonate without decomposition.

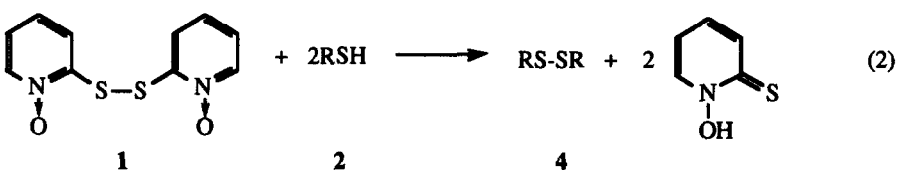
Attempts to prepare a mixed disulfide, **3**, from some thiols failed. Instead, a symmetrical disulfide, **4**, was obtained (Equation 2). For example, the addition of 2-thiopyridine, **2f**, to disulfide, **1**, in dichloromethane immediately gave dipyridyl disulfide, **4ff**, even with slow addition of the thiol at low temperature (0°C). Likewise, sulfide dimers were obtained with mercaptoacetic acid (thioglycolic acid), **2b**, thiophenol, **2d**, 2-methoxythiophenol, **2e**, and thiobenzoic acid, **2g**.

Table 1. Synthesis of Unsymmetrical Disulfides, **3**, from Disulfide, **1**, and Thiols (RSH), **2**.

R	Thiol (RSH)	 **3**	Time (hr)	Yield (%)
R = nC_3H_7	**2a**	**3a**	30	100*
R = CH_2COOH	**2b**	**3b**	12	98
R = $CH_2CH(NHAc)COOH$	**2c**	**3c**	30	96*
R = C_6H_5	**2d**	**3d**	1.5	95*
R = C_6H_5 (2-OMe)	**2e**	**3e**	1	91

*One to four equivalents of acetic acid were used to promote the reaction.

Equation 2



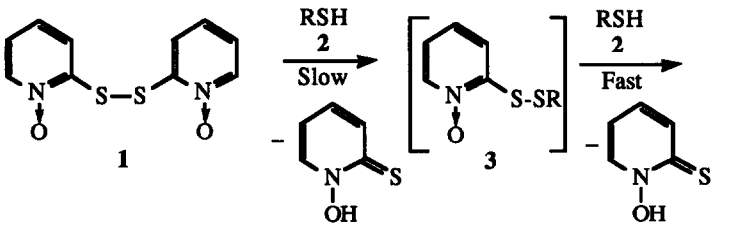
1 **2** **4**

(2)

2b, 4bb	R = CH_2COOH
2d, 4dd	R = C_6H_5
2e, 4ee	R = C_6H_5 (2-OMe)
2f, 4ff	R = C_5H_4NS
2g. 4gg	R = C_7H_5O

Apparently, in these sulfur-exchange reactions, a pyridine N-oxide intermediate (mixed disulfide), **3**, served as an extremely reactive sulfenylating agent itself to give the symmetrical disulfide, **4**, and thiohydroxamic acid (Equation 3). Prolonged reaction times and two equivalents of the thiol were necessary to prepare disulphidoacetic acid, **4bb**, and 2,2'-dimethoxyphenyl disulfide, **4ee**. The syntheses of symmetrical disulfides from **1** and various thiols are described in Table 2.

Equation 3



(3)

Table 2. Synthesis of Symmetrical Disulfides (RSSR), **4**, from Disulfide, **1** and Thiols (RSH), **2**.

R	Thiol (RSH) **2**	Disulfide (RS-SR) **4**	Time (hr)	Yield[a] (%)
$R = CH_2COOH$	**2b**	**4bb**	18	100[b]
$R = C_6H_5$	**2d**	**4dd**	54	92
$R = C_6H_5$ (2-OMe)	**2e**	**4ee**	1	81
$R = C_5H_4N$	**2f**	**4ff**	1	100
$R = C_7H_5O$	**2g**	**4gg**	1	94

[a]Isolated yield; [b]Yield was determined by NMR

The use of the mixed disulfide, **3**, as a general reagent to prepare unsymmetrical disulfides, often a difficult problem in organosulfur chemistry, was recognized. Its ease of preparation and handling were especially attractive. Therefore, the sulfenylating ability of mixed disulfide **3** was investigated further. Treatment of alkyl (n-propyl, **3a**) or aryl (C_6H_5, **3d**) **3** with various thiols in dichloromethane or chloroform at room temperature gave the desired unsymmetrical disulfides, **4** (Equation 4), in moderate to high yields, as summarized in Table 3.

The sulfenylation of thiols **2b**, **2d**, and **2f** with **3a** proceeded well and gave very good yields of **4ab**, **4ad** and **4af**, respectively (Table 3). In the reaction of thiobenzoic acid, **2g**[18], the yield of desired unsymmetrical disulfide, **4ag**, was only 32%. Three other products were also isolated: n-propyl disulfide, **4aa** (30%), propyl pyridyl disulfide, **4af** (34%)[19], and dibenzoyl disulfide, **4gg** (64%). These byproducts came from oxidation-reduction of the thiol and pyridine-N-oxide. Sulfenylation of N-acetyl-L-cysteine, **2c**, with **3a** gave a 32% yield of desired disulfide **4ac**. In this reaction, most of the cysteine was recovered while **3a** was decomposed to propyl disulfide, among other products. Compound **3c** was inert to sulfenylation. It was totally recovered after being mixed with n-propylthiol or thiophenol in dichloromethane for up to 4 days. 2-Phenyldithiopyridine-N-

oxide, **3d**, proved to be a good sulfenylation agent. It reacted with thiols to give unsymmetrical disulfides in very high yields. All of these results are summarized in Table 3.

Table 3. Synthesis of Unsymmetrical Disulfides (RSSR'), **4**, from Mixed Disulfide, **3**, and Thiols, (RSH), **2**.

R	R'	Thiol (R'SH)	Disulfide (RSSR')	Time (hr)	Yield (%)
R = nC_3H_7	R' = CH2COOH	**2b**	**4ab**	23	100[a,b]
R = nC_3H_7	R' = AcCys[c]	**2c**	**4ac**	40	96[a]
R = nC_3H_7	R' = C_5H_4N	**2f**	**4af**	18	89[a]
R = nC_3H_7	R' = C_7H_5O	**2g**	**4ag**	48	32[a,e]
R = nC_3H_7	R' = C_6H_5	**2d**	**4ad**	72	32[d]
R = C_6H_5	R' = nC_3H_7	**2a**	**4ad**	48	100[d]
R = C_6H_5	R' = CH_2COOH	**2b**	**4db**	24	97[a]
R = C_6H_5	R' = C_6H_5	**2d**	**4dd**	48	91[d,f]
R = C_6H_5	R' = C_5H_4N	**2f**	**4df**	24	86[a,g]

a) Isolated Yield; b) The conversion was 57% in 6 hours determined by NMR; c) AcCys=$CH_2CH(NH)COOH$; d)Yield determined by NMR; e) Di-n-propyldisulfide, **4aa** (15%), n-propyl 2-pyridyl disulfide, **4af** (34%), and dibenzoyl disulfide, **4gg** (39%), were also isolated; f) Starting material **3d** (9%) was detected; g) Sulfenylating agent **3c** was prepared *in situ* and was not isolated from thiohydroxamic acid.

Equation 4

(4)

3 2 4

3a R = nC_3H_7
3d R = C_6H_5
3c R = AcCys*

2b R' = CH_2COOH
2c R'= AcCys*
2d R'= C_6H_5
2f R'= C_5H_4N
2g R'= C_7H_5O

4aa R = R' = nC_3H_7
4ab R = nC_3H_7, R' = CH_2COOH
4ac R = nC_3H_7, R' = AcCys*
4ad R = nC_3H_7, R' = C_6H_5
4af R = nC_3H_7, R' = C_5H_4N
4ag R = nC_3H_7, R' = C_7H_5O
4db R = C_6H_5, R' = CH_2COOH
4dd R = C_6H_5, R' = C_6H_5
4df R = C_6H_5, R' = C_5H_4N
4gg R = R' = C_7H_5O

*AcCys = $CH_2CH(NHAc)COOH$

In conclusion, the alkyl and aryldithiopyridine N-oxides were shown to be good sulfenylating agents for other thiols. These compounds were easily prepared and handled. The reactions discussed have provided practical and convenient general methods for the preparation of symmetrical and unsymmetrical disulfides from thiols.

EXPERIMENTAL

Proton (^1H) and carbon (^{13}C) NMR spectra were obtained using either a Varian XL-200E or Varian Gemini-200 spectrometer. Compounds for NMR analysis were dissolved in deuteriochloroform solution with tetramethylsilane ($CDCl_3$/TMS) as the internal standard or in deuterium oxide (D_2O). All NMR chemical shifts were reported in δ units (ppm). Infrared spectra (IR) of either "neat" oils, potassium bromide pellets (KBr), chloroform ($CHCl_3$) or dichloromethane (CH_2Cl_2) solutions were obtained using a Perkin-Elmer 881 spectrophotometer and the lambda-max values were reported in reciprocal centimeters (cm^{-1}). Mass spectra (MS) were obtained using a Hewlett-Packard 5995c quadrapole GC-MS instrument. Elemental analyses (microanalyses) were performed at Atlantic Microlab, Atlanta, Georgia. Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. The term *in vacuo* refers to water aspirator vacuum. Chromatographic separations were performed by either (a) preparative radial chromatography (chromatotron) with Analtech silica gel GF (1000 μ) plates, (b) column chromatography with Aldrich silica gel, 130-270 mesh, 60 angstrom, or (c) reversed-phase high pressure liquid chromatography (RP-HPLC). The RP-HPLC system used for the analysis of **3c** consisted of a Waters Associates Model 600E pump, Lambda-Max Model 481 ultraviolet detector, Model 710 Wisp autoinjector and a Spectra physics 4270 integrator. The gradient mobile phase was a two component system: mobile phase A, 0.1M ammonium acetate; mobile phase B, 0.1M ammonium acetate in methanol (HPLC grade).

2,2'-Dithiodipyridine-1,1'-dioxide, 1: Compound **1** was prepared by oxidation of 2-mercaptopyridine-1-oxide[12]. In an improved procedure, a suspension of 42.3 g of 2-mercaptopyridine-1-oxide in water (300 ml) was treated with 30% hydrogen peroxide (35 ml). The reaction was slightly exothermic. The reaction mixture was stirred for 1 hour with the temperature maintained at 45°C. A white solid, 34.6 g (81%), was collected by suction filtration, mp 200-201°C. Recrystallization from methanol gave a white crystal, mp 205-206°C.

2-n-Propyldithiopyridine-N-oxide, 3a: 2,2'-Dithiodipyridine-1,1'-dioxide, **1** (1.256 g, 5.0 mmol), n-propylthiol , **2a** (380 mg, 5 mmol), and acetic acid (1.2 g, 20 mmol) were dissolved in dichloromethane (25 ml) and stirred at room temperature for 30 hours. The mixture was diluted with dichloromethane to 60 ml and washed successively with 5% aqueous NaOH (25 ml) and H_2O (20 ml). The aqueous phase was extracted with dichloromethane (2 X 20 ml). The combined extract was concentrated *in vacuo* and a colorless oil was obtained (1.10 g, 100%). Treatment of this oil with diethyl ether (10 ml) before it solidified gave a white crystal (830 mg) which was collected by suction filtration, mp 82-84°C. Another 175 g of the compound was obtained from the mother liquid; ^1H-NMR ($CDCl_3$/TMS) δ (ppm) 0.99 (t, J 7.3 Hz, 3H, Me), 1.70 (tq, J 7.3 Hz, 2H, $-CH_2-$), 2.72 (t, J 7.3 Hz, 2H, $-CH_2S-$), 7.20 (ddd, J 1.7, 6.8, 6.1 Hz, 1H, Py), 7.49 ddd, J 1.4, 8.4, 6.8 Hz, 1H, Py); ^{13}C-NMR ($CDCl_3$) δ (ppm) 12.99, 22.39, 40.04, 121.62 (two carbons), 126.16, 138.51, 152.04; IR (CH_2Cl_2) (cm^{-1}) 3044, 2969, 1463, 1420, 1258, 894, 732; MS (EI) m/e (relative intensity): 201 (M^+, 18.9%)

159 (23.3), 142 (10.8), 127 (100), 111 (100), 78 (100); Anal. ($C_8H_{11}NOS_2$) C (calc. 47.73, found 47.82), H (calc. 5.51, found 5.51), N(calc. 6.96, found 7.04), S (calc. 31.86, found 31.95).

2-Carbohydroxymethyldithiopyridine-N-oxide, 3b: 2,2'-Dithiodipyridine-1,1'-dioxide, **1** (1.26 g, 5.0 mmol) and 2-mercaptoacetic acid, **2b** (452 mg, 5.5 mmol), were dissolved in dichloromethane (40 ml) and stirred at room temperature for 12 hours. A white solid was deposited. The solution was concentrated *in vacuo* to about 20 ml and the solid was collected by filtration. Another portion of solid was deposited when the mother liquid was left standing for two days[20]. The total amount of solid product was 1.061 g (98% yield), mp 124°C; ^{1}H-NMR ($CDCl_3$/TMS) δ (ppm) 3.45 (s, 2H, -CH_2-), 7.31 (ddd, J 1.7, 6.2, 6.2 Hz, 1H, Py), 7.64 (dd, J 6.2, 8.4 Hz, 1H, Py), 8.05 (dd, J. 1.7, 8.4 Hz, 1H, Py), 8.21 (d, J 6.2 Hz, 1H, Py); ^{13}C-NMR $CDCl_3$) δ (ppm) 45.78, 125.94, 134.54, 141.97, 154.67, 178.61; IR (KBr) (cm^{-1}) 1703; MS(EI) m/e (relative intensity): 201 (M^+-16, 0.8%), 182 (37.4), 164 (10.7), 156 (8.2), 137 (5.7), 127 (92.8), 11 (100); Anal. ($C_7H_7NO_3S_2$) C (calc. 38.70, found 38.80), H (calc. 3.25, found 3.26), N (calc. 6.45, found 6.44), S (calc. 29.52, found 29.62).

2-Pyridyl-L-(N-acetyl)cystine-1-oxide, 3c. A. Using Organic Solvent: A mixture of 2,2'-dithiodipyridine-1,1'-dioxide, **1** (2.52 g, 10.0 mmol), N-acetyl-L-cysteine, **2c** (1.63 g, 10.0 mmol), and acetic acid (1.8 g, 30 mmol) in chloroform (120 ml) was stirred at room temperature for about 30 hours. The solid which formed was collected by suction filtration and the crude product (2.46 g, 96%) was recrystallized from methanol to give 2.46 g of white crystalline material (86%), mp 184-186°C (Unpublished data[2], 191-192°C); ^{1}H-NMR (D_20) δ (ppm) 1.92 (s, 3H, $C\underline{H}_3$), 3.09 (dd, J 8.8, 12.5 Hz, 1H, noneqiuv. -$C\underline{H}_2$-), 3.31 (dd, J 4.2, 12.5 Hz, 1H, noneqiuv. -$C\underline{H}_2$-), 4.52 (m, 1H, -CHN=), 7.32 (t, J 7.2 Hz, 1H, Py), 7.63 (tm, J 7.9 Hz, 1H, Py), 7.98 (dm, J 8.8 Hz, 1H, Py), 8.22 (dm, J 7.2 Hz, 1H, Py); ^{13}C-NMR (D_2O) δ (ppm) 24.55 ($CO\underline{C}H_3$), 41.40 (ß-$\underline{C}H_2$), 54.96 ($\underline{C}$HNH), 126.01 (C_3 & C_5), 134.40 (C_4), 141.99 (C_6), 154.47 (C_2), 176.07 and 177.04 ($\underline{C}$O & $\underline{C}$OOH); Anal. ($C_{10}H_{12}N_2O_4S_2$) C (calc. 41.65, found 41.68), H (calc. 4.19, found 4.15), N (calc. 9.72, found 9.69), S (calc. 22.24, found 22.32). **B. Using Aqueous Solvent:** A slurry of 2,2'-dithiodipyridine-1,1'-dioxide, **1** (2.53 g, 10.0 mmol) was treated with a solution of N-acetyl-L-cysteine, **2c** (1.63 g, 10.0 mmol), in H_2O (10 ml). The solution became clear in about 30 minutes and stirring was continued for 24 hours at room temperature. Analysis by RP-HPLC (gradient from 100% mobile phase A to 30:70 A/B in 20 minutes) revealed that product **3c** was formed in 64% yield by comparison to synthetic standard prepared above.

2-Phenyldithiopyridine N-oxide, 3d: 2,2'-Dithiodipyridine-1,1'-dioxide, **1** (1.26 g, 5.0 mmol) was dissolved in dichloromethane (20 ml) and acetic acid (330 mg, 5.5 mmol). Thiophenol, **2b** (550 mg, 5.0 mmol), was added and the mixture was stirred at room temperature for 1.5 hours. The solution was diluted to 60 ml with dichloromethane, washed with 5% aqueous NaOH (30 ml) and water (30 ml), and the aqueous phase was extracted with dichloromethane (2 X 20 ml). The combined extract was dried over sodium sulfate and concentrated *in vacuo* to give a colorless oil (1.2 g, 95%) which solidified after several hours, mp 58-61°C[21]; ^{1}H-NMR ($CDCl_3$/TMS) δ (ppm) 7.07 (t, J 7.1 Hz, 1H, Py), 7.22 (m, 4 H), 7.41 (dd, J 6.1, 0.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 122.37, 122.52, 126.84, 128.17 (two carbons), 128.25, 129.81 (two carbons),

134.80, 139.00, 151.77; IR (neat) (cm^{-1}) 3059, 1575, 1463, 1420, 1258, 1221, 1135, 1077, 837, 745, 687; MS (EI) m/e (relative intensity): 235 (M^+, 6.1%), 219 (15.0), 186 (100) 125 (64.9) 109 (69.2), 78 (100).

2-(2-Methoxyphenyldithio)pyridine N-oxide, 3e: To a suspended solution of 2,2'-dithiodipyridine-1,1'-dioxide, **1** (189 mg, 0.75 mmol) in dichloromethane (20 ml), acetic acid (150 mg, 1.0 mmol) was added and stirred until **1** dissolved. A solution of 2-methoxythiophenol, **2d** (105 mg, 0.75 mmol), in dichloromethane (5 ml) was added slowly. The mixture was stirred for 1 hour at room temperature, diluted with dichloromethane to 40 ml and the solution was washed with 5% aqueous NaOH (20 ml) and H_2O (10 ml). The aqueous phase was extracted with dichloromethane (15 ml). The combined organic phase was evaporated *in vacuo* to give a white crystalline material (195 mg, 91% yield), mp 92-95°C; ^{1}H-NMR ($CDCl_3$) δ (ppm) 3.85 (s, 3H), 6.86 (m, 2H), 7.07 (tm, J 6,.4 Hz, 1H), 7.22 (m, 2H), 7.41 (dm, J 8.0 Hz, 1H), 7.78 (dm, J 8.0 Hz, 1H), 8.18 (dm, J 6.4 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 55.89, 110.91, 121.41, (two carbons), 121.81, 122.34, 126.27, 128.95, 129.08, 138.45, 151.51, 157.31; IR ($CHCl_3$) (cm^{-1}) 1578, 1463, 1420, 1241, 1020, 749; MS (EI) m/e (relative intensity): 265 (M^+, 6.2%), 249 (21.1), 220 (1407), 186 (75.4), 78 (100).

Disulphidoacetic Acid, 4bb: 2,2-Dithiodipyridine-1,1'-dioxide, **1** (31.5 mg, 0.125 mmol) and mercaptoacetic acid, **2b** (26 mg, 0.25 mmol) were dissolved in $CDCl_3$ (0.7 ml) in an NMR tube. The reaction gave quantitative yields of **4bb**[21] and thiohydroxamic acid after 18 hours at room temperature, as determined by NMR. NMR signals for **4bb** were as follows; ^{1}H-NMR ($CDCl_3$) ∂ (ppm) 3.64 (s, 2H, -CH_2-), 10.47 (br s, 1H, COOH); ^{13}C-NMR ($CDCl_3$) ∂ (ppm) 42.89, 178.20.

Diphenyl Disulfide, 4dd: (a) Using 1 and Thiophenol: 2,2'-Dithiodipyridine-1,1'-dioxide, **1** (252 mg, 1.0 mmol), acetic acid (60 mg, 1.0 mmol) and thiophenol, **2d** (230 mg, 2.1 mmol), in dichloromethane were stirred at room temperature for 54 hours. The mixture was diluted with dichloromethane to 40 ml and washed successively with 5% aqueous NaOH and H_2O (10 ml each). The aqueous phase was extracted with dichloromethane (15 ml). The combined organic phase was dried over sodium sulfate and concentrated *in vacuo* to give a colorless oil (201 mg, 92%) which solidified upon standing, mp 58-60°C[21]; ^{1}H-NMR ($CDCl_3$) δ (ppm) 7.29 (m, 6H), 7.54 (dd, J 1.6, 8.0 Hz, 4H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 127.71, 128.10, 129.61, 137.60; IR (neat) (cm^{-1}) 3070, 1571, 1473, 1433, 1067, 1020, 734, 685; **(b) Using 3d and Thiophenol:** 2-Phenyldithiopyridine N-oxide, **3d** (59 mg, 0.25 mmol), and thiophenol, **2d** (30 mg, 0.273 mmol), were dissolved in $CDCl_3$ in an NMR tube. The reaction gave 91% of **4dd** (spectral data given above) and thiohydroxamic acid after 2 days at room temperature.

Di-(2-methoxyphenyl)disulfide, 4ee: 2,2'-Dithiodipyridine-1,1'-dioxide, **1** (252 mg, 1.0 mmol), and 2-methoxythiophenol, **2e** (295 mg, 2.1 mmol), were mixed in chloroform (8 ml). The compounds dissolved after several minutes and the mixture was stirred at room temperature for 1 hour. The chloroform was evaporated *in vacuo* and diethyl ether was added. Product was precipitated after several hours and collected by filtration as white needles (225 mg, 81% yield), mp 114-116°C; ^{1}H-NMR ($CDCl_3$/TMS) δ (ppm) 3.88 (s, 6H), 6.87 (m,

4H), 7.17 (dt, J 1.3, 7.8 Hz, 2H), 7.52 (dd, J 1.6, 7.8 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 56.38, 111.05, 121.83 (two carbons), 128.15, 128.28, 157.12; IR ($CHCl_3$) (cm^{-1}) 1577, 1471, 1270, 1236, 1021, 729.

Di-(2-pyridyl)disulfide, 4ff: A. Typical Experiment: 2-Thiopyridine, **2f** (550 mg, 5.0 mmol), was added to a suspended solution of 2,2'-dithiodipyridine-1,1'-dioxide, **1** (1.26 g, 5.0 mmol), in chloroform (30 ml). The mixture was stirred at room temperature for several minutes and a clear yellow solution was formed. After 1 hour, the solution was concentrated by evaporating the solvent *in vacuo*. Diethyl ether (30 ml) was added, a white crystalline material deposited immediately and was collected by filtration as compound **1**, (598 mg, 47%). The mother liquid was diluted with dichloromethane (50 ml) and the solution was washed with 5% aqueous NaOH (20 ml) and H_2O (15 ml). The aqueous phase was extracted with dichloromethane (20 ml). The combined extract was concentrated to give a colorless oil (550 mg, 100%) which solidified upon standing[22]; ^{1}H-NMR ($CDCl_3$/TMS) δ (ppm) 7.19 (m, 2H), 7.57 (m, 4H), 8.43 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 120.13, 121.57, 137.81, 140.95, 159.27; IR ($CHCl_3$) (cm^{-1}) 1571, 1558, 1445, 1416, 1115, 717.
B. *In Situ* Experiment: The following experiment was carried out in a NMR tube: **1** (32 mg, 0.125 mmol) and **2d** (30 mg, 0.27 mmol) were dissolved in $CDCl_3$ (0.65 ml). The proton NMR spectra obtained after 30 minutes at room temperature indicated the presence of di-(2-pyridyl)disulfide and thiohydroxamic acid in quantitative yields.

Dibenzoyl disulfide, 4gg: Thiobenzoic acid, **2g** (1.38 g, 10 mmol), was added to a suspension of 2,2'-dithiodipyridine-1,1'-dioxide, **1** (1.26 g, 5.0 mmol), in dichloromethane (25 ml). A clear solution was formed after the mixture was stirred at room temperature for 1 hour. The yellow solution was concentrated *in vacuo* and the residue was chromatographed on a silica gel column. A yellowish solid was obtained (1.324 g, 97%). Recrystallization from dichloromethane-diethyl ether gave an almost white crystal[21], mp 119-121°C; ^{1}H-NMR ($CDCl_3$/TMS) δ (ppm) 7.48 (t, J 7.4 Hz, 2H), 7.62 (m, 1H), 8.04 (dd, J 7.0, 1.6 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 128.59 (two carbons), 129.48 (two carbons), 134.88, 135.72, 186.53; IR (neat) (cm^{-1}) 1677, 1202, 882, 673.

n-Propyldithioacetic Acid, 4ab: 2-n-Propyldithiopyridine N-oxide, **3a** (201 mg, 1.0 mmol), and mercaptoacetic acid, **2b** (102 mg, 1.1 mmol), were dissolved in chloroform (10 ml) and stirred at room temperature for 23 hours. The reaction mixture was concentrated *in vacuo* and the residue was chromatographed on a silica gel plate (chromatotron) using a mobile phase of ethyl acetate-methanol. Compound **4ab** was obtained as a colorless oil (165 mg, 100%); ^{1}H-NMR ($CDCl_3$/TMS) δ (ppm) 1.00 (t, J 7.3 Hz, 3H, Me), 1.72 (tq, J 7.3, 6.9 Hz, 2H, -CH_2-), 2.76 (t, J 6.9 Hz, 2H, -CH_2S-), 3.50 (s, 2H, -CH_2-S-), 9.60 (br s, OH); ^{13}C-NMR ($CDCl_3$) δ (ppm) 13.30, 22.45, 40.73, 44.41, 178.40; IR (neat) (cm^{-1}) 1703.

S-(N-Propylthio)-N-acetyl-L-cysteine, 4ac: 2-(n-Propyldithio)pyridine N-oxide, **3a** (100 mg, 0.5 mmol), and N-acetyl-L-cysteine, **2c** (98 mg, 0.6 mmol), were dissolved in a mixed solvent (10 ml) of dichloromethane-methanol (8:2). The solution was stirred at room temperature for 3 days. The solvents were evaporated *in vacuo* and the residue was analyzed by NMR to reveal the presence of desired disulfide, **4ac** (32%

yield), along with other products; ^{1}H-NMR ($CDCl_3$/TMS) δ (ppm) 1.05 (s, 3H), 1.73 (m, 2H), 2.17 (s, 3H), 2.88 (t, J 7.2 Hz, 2H), 3.15 (m, 1H), 3.35 (m, 1H), 4.86 (m, 1H).

n-Propyldithiobenzene, 4ad: (a) Using 3a and Thiophenol: 2-(n-Propyldithio)pyridine N-oxide, **3a** (205 mg, 1.2 mmol), and thiophenol, **2d** (120 mg, 1.1 mmol), were dissolved in dichloromethane (8 ml) and stirred at room temperature for about 40 hours. The mixture was diluted with dichloromethane to about 40 ml and washed successively with 3% aqueous NaOH (15 ml) and H_2O (10 ml). The aqueous phase was extracted with dichloromethane (2 X 15 ml). The combined organic extract was concentrated *in vacuo* and the residue was chromatographed through a short silica gel column to yield product **4ad**[23] as a colorless oil (177 mg, 96% yield); ^{1}H-NMR ($CDCl_3$/TMS) δ (ppm) 0.97 (t, J 7.3 Hz, 3H), 1.70 (tq, 7.3, 7.3 Hz, 2H), 2.72 (t, J 7.3 Hz, 2H), 7.27 (m, 3H), 7.55 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 13.59, 22.68, 41.42, 127.11, 127.85, 129.41, 138.20; IR (neat) (cm^{-1}) 3055, 2964, 1577, 1475, 1437, 1289, 1230, 1022, 738, 687; **(b) Using 3d and n-Propylthiol:** 2-Phenyldithiopyridine N-oxide, **3d** (59 mg, 0.25 mmol), and n-propylthiol, **2a** (21 mg, 0.275 mmol), were dissolved in $CDCl_3$ (0.7 ml) in an NMR tube. The reaction gave 31% of the desired product after 18 hours at room temperature. Quantitative yields of n-propyldithiobenzene, **4ad** (spectral data given above), and thiohydroxamic acid were observed after 48 hours.

2-(n-Propyldithio)pyridine, 4af: 2-(n-Propyldithio)pyridine N-oxide, **3a** (201 mg, 1.0 mmol), and 2-thiopyridine, **2f** (140 mg, 1.3 mmol), were dissolved in chloroform (10 ml) and stirred at room temperature for 18 hours. The mixture was diluted with dichloromethane to about 40 ml and washed successively with 3% aqueous NaOH (15 ml) and H_2O (10 ml). The aqueous phase was extracted with dichloromethane (2 X 15 ml). The combined organic extract was concentrated *in vacuo* and the residue was purified by chromatography on a silica gel column. Product, **4af**, was isolated as a colorless oil (165 mg, 89%)[24]; ^{1}H-NMR ($CDCl_3$/TMS) δ (ppm) 0.97 (t, J 7.3 Hz, 3H), 1.70 (tq, J 7.3, 7.3 Hz, 2H), 2.76 (t, J 7.3 Hz, 2H), 7.02 (m, 1H), 7.60 (m, 2H), 8.40 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 13.55, 22.75, 41.41, 120.01, 120.95, 137.48, 149.91, 161.14; IR (neat) (cm^{-1}) 2693, 1233, 1208.

Benzoyl n-Propyl Disulfide, 4ag: 2-(n-Propyldithio)pyridine N-oxide, **3a** (402 mg, 2.0 mmol), and thiobenzoic acid, **2g** (305 mg, 2.2 mmol) ,were dissolved in dichloromethane (10 ml) and the mixture was stirred at room temperature for two days. The mixture was concentrated *in vacuo* and the residue was chromatographed on a silica plate. The following compounds were eluted with a mobile phase of hexane-ethyl acetate:

(a) Di-n-propyl Disulfide, 4aa, as a colorless oil (45 mg, 15% yield)[25]; ^{1}H-NMR ($CDCl_3$/TMS) δ (ppm) 0.99 (t, J 7.2 Hz, 6H), 1.78 (tq, J 7.2, 7.2 Hz, 4H), 2.90 (t, J 7.2 Hz, 4H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 13.55, 22.68, 41.87; IR (neat) (cm^{-1}) 2959, 1451, 1231;

(b) Dibenzoyl Disulfide, 4gg, as a yellowish needle (193 mg, 39% yield), mp 118°C[22]; ^{1}H-NMR ($CDCl_3$/TMS) δ (ppm) 7.58 (m, 4H), 7.71 (m, 2H), 8.05 (m, 4H);

(c) Benzoyl n-Propyl Disulfide, 4ag, as a colorless oil (136 mg, 32% yield); ^{1}H-NMR ($CDCl_3$/TMS) δ (ppm) 1.01 (t, J 7.1 Hz, 3H), 1.69 (tq, J 7.1 Hz, 2H), 2.75 (t, J 7.1 Hz, 2H), 7.74 (m, 2H), 7.58 (m, 1H),

7.98 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 13.06, 22.74, 40.72, 127.68 (two carbons), 128.84 (two carbons), 133.97, 135.77, 190.51, IR (neat) (cm^{-1}) 2931, 1689;

(d) n-Propyl 2-Pyridyl Disulfide, 4af, as a colorless oil (125 mg, 34% yield)[24] ^{1}H-NMR ($CDCl_3$/TMS) δ (ppm) 0.96 (t, J 7.2 Hz, 3H), 1.67 (tq, J 7.23 Hz, 2H), 2.74 (t, J 7.2 Hz, 2H), 7.02 (m, 1H), 7.60 (m, 2H), 8.40 (m, 1H).

Phenyldithioacetic Acid, 4db: 2-Phenyldithiopyridine N-oxide, **3d** (235 mg, 1.0 mmol), and mercaptoacetic acid, **2b** (100 mg, 1.1 mmol), were dissolved in dichloromethane (8 ml), and stirred at room temperature for 24 hours. The mixture was concentrated by evaporating the solvent *in vacuo* and the residue was chromatographed on a silica gel column to obtain a colorless oil (194 mg, 97% yield) which solidified on standing, mp 40°C (41°C)[26]; ^{1}H-NMR ($CDCl_3$/TMS) δ (ppm) 3.49 (s, 2H), 7.25 (m, 3H), 7.51 (s, 2H), 11.50 (br s, 1H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 43.63, 127.41, 128.92, 129.51 (two carbons), 129.55, 138.20; IR (neat) (cm^{-1}) 1707.

2-Phenyldithiopyridine, 4df: A solution of 2,2'-dithiodipyridine-1,1'-dioxide, **1** (630 mg, 2.5 mmol), acetic acid (150 mg, 2.5 mmol) and thiophenol, **2d** (550mg, 2.5 mmol), in chloroform (20 ml) was stirred at room temperature for 1.5 hours. 2-Thiopyridine, **2f** (275 mg, 2.5 mmol), was added and the mixture was stirred for another 24 hours. The solution was then diluted with dichloromethane to 50 ml and washed with 5% aqueous NaOH (20 ml). The combined organic phase was dried over sodium sulfate and concentrated *in vacuo* to yield a colorless oil (552 mg, 100%). An analytical sample was obtained by chromatography on silica gel (chromatotron) as a colorless oil (86%)[27]; ^{1}H-NMR ($CDCl_3$/TMS) δ (ppm) 7.02 (m, 1H), 7.21 (m, 3H), 7.42-7.60 (m, 4H), 8.39 (dm, J 5.3 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 120.06, 121.40, 127.77, 127.82, 129.54, 129.62, 137.75, 137.85, 150.00, 160.09; IR (neat) (cm^{-1}) 3047, 1569, 1444, 1415, 1259, 1115, 758, 740.

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