A Mild and Environmentally Benign Oxidation of Thiols to Disulfides

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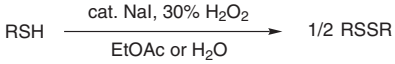
Abstract: Thiols were effectively oxidized into disulfides by reacting with hydrogen peroxide in the presence of a catalytic amount of iodide ion or iodine.

Key words: thiol, disulfide, oxidative coupling, hydrogen peroxide, iodide catalyst

The controlled oxidative coupling of thiols to disulfides is important in organic synthesis, and a wide range of methods have been developed for this transformation.[1] Thiols are among the functional groups which can be easily over oxidized, therefore, extensive studies have been carried out for their controlled oxidation with molecular oxygen,[2] peroxide,[3] metal oxidants,[4] halogens and derivatives,[5] sulfoxide,[6] and *N*-oxide.[7] In particular, the methods of oxidative coupling of disulfides with halogens such as I_2,[5a] I_2/HI,[5b] and Br_2/$KHCO_3$[5c] were carried out under mild reaction conditions, and gave the disulfides in good yields. However, these reactions require a stoichiometric amount of oxidants and long reaction times. Oae and co-workers developed the oxidative coupling of thiols to disulfides by dimethyl sulfoxide in the presence of a catalytic amount of molecular iodine.[5b] Although this reaction affords the products in high yield under very mild reaction conditions, there are still some problems such as the requirement of a long reaction time and the production of foul-smelling dimethyl sulfide as a waste product.

To develop an environmentally benign oxidative coupling of thiols, we planned to use hydrogen peroxide as a co-oxidant for the oxidation of thiols with molecular iodine, because the iodide ion (iodoanion) is easily oxidized to molecular iodine by hydrogen peroxide.

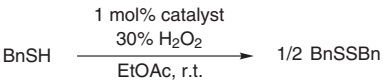
Hydrogen peroxide itself can oxidize thiols to the corresponding disulfides; however, alkaline conditions were required.[3a] Recently, Bégué et al. reported that disulfides can be efficiently prepared from thiols using 30% hydrogen peroxide in fluoroalcohols at ambient temperature under neutral conditions.[3b] Although this method provides the desired compounds in high yields in most cases, fluoroalcohols are expensive for industrial use. Furthermore, the thiols, which are less soluble in the fluoroalcohols, produced the desired disulfides in poor yields. In this paper, we describe a method for the oxidation of thiols **1** to disulfides **2** using 30% hydrogen peroxide catalyzed by iodide ion (Scheme 1).



Scheme 1

We first investigated the catalysts needed for the oxidation of benzyl mercaptan to dibenzyl disulfide.[8] Benzyl mercaptan was dissolved in ethyl acetate and treated with 1.0 equivalent of 30% hydrogen peroxide in the presence or absence of 1 mol% of catalyst (sodium iodide, potassium bromide or iodine) at room temperature (Table 1). Sodium iodide and iodine were good catalysts for this reaction and provided the desired compound in excellent yields with a shorter reaction time (0.5 h). On the other hand, potassium bromide afforded the disulfide in a moderate yield with a longer reaction time (26 h). Without the catalyst under otherwise identical conditions, the yield was lowest with a long reaction time (24 h).

Table 1 Reaction of Benzyl Mercaptan with 30% H_2O_2



Run	Catalyst	Time (h)	Yield (%)
1	NaI	0.5	96
2	KBr	26	63
3	I_2	0.5	99
4	–	24	26

Several kinds of thiols were treated with 1 mol% sodium iodide and 1.0 equivalent of 30% hydrogen peroxide in ethyl acetate at room temperature (Table 2). Both alkyl and aryl disulfides were obtained in high yields with short reaction times (0.5 h). In the case of a sterically hindered thiol, the reaction was very slow and provided the disulfide in low yield (entry 5).

We further examined the reaction without an organic solvent. These results are summarized in Table 3. In most cases, it took a longer time to complete the reaction (24 h) because of the solubility problem; however, the desired

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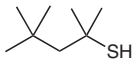
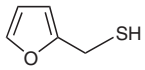
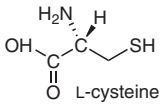
Table 2 Reaction of Thiols with H_2O_2 (1.0 equiv) Catalyzed by NaI (1 mol%) in EtOAc

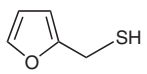
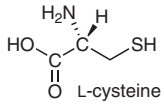
RSH —(1 mol% NaI, 1.0 equiv H_2O_2; EtOAc, r.t.)→ 1/2 RSSR

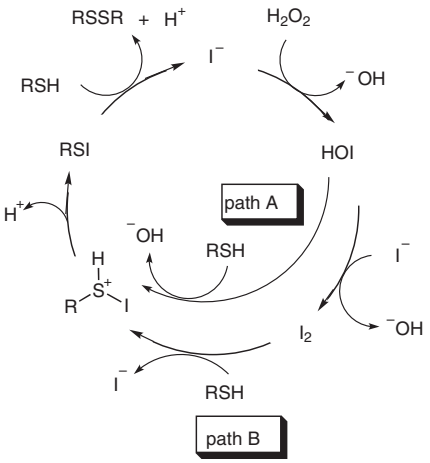
Entry	RSH	Time (h)	Yield (%)
1	BnSH	0.5	96
2	*n*-BuSH	0.5	92
3	$CH_3(CH_2)_{11}SH$	0.5	97
4	*c*-HexSH	0.5	97
5		24	28
6		0.5	98
7	4-MeC_6H_4SH	0.5	99
8	4-ClC_6H_4SH	0.5	92
9	4-$O_2NC_6H_4SH$	0.5	93
10	 L-cysteine	0.5	87

disulfides were also obtained in high yields. It is noteworthy that L-cysteine was almost quantitatively oxidized to L-cystine (entry 9). The reaction of L-cysteine with 30% hydrogen peroxide in a fluoroalcohol afforded L-cystine in a poor yield due to the solubility problem of L-cysteine in the fluoroalcohol.[3b] Our result is in sharp contrast to this.

Table 3 Reaction of Thiols with H_2O_2 (1.0 equiv) Catalyzed by NaI (1 mol%) in H_2O

RSH —(1 mol% NaI, 1.0 equiv H_2O_2; EtOAc, r.t.)→ 1/2 RSSR

Entry	RSH	Time (h)	Yield (%)
1	BnSH	24	94
2	$CH_3(CH_2)_3SH$	24	92
3	$CH_3(CH_2)_{11}SH$	24	97
4	*c*-HexSH	24	94
5		24	98
6	4-MeC_6H_4SH	24	93
7	4-ClC_6H_4SH	24	99
8	4-$O_2NC_6H_4SH$	24	95
9	 L-cysteine	0.5	95



Scheme 2

The mechanism for this reaction is depicted in Scheme 2. The iodide ion (I^-) is oxidized into active iodine cationic species (HOI) by hydrogen peroxide. The reaction of I^+ equivalent (HOI) with a thiol affords the intermediate iodosulfonium compound either by path A or the former reacts with unreacted I^- to form molecular iodine which then reacts with a thiol (path B). The iodosulfonium compound then couples with a thiol to provide the disulfide and the iodide ion.

In conclusion, thiols can be oxidized to disulfides by 1.0 equivalent of 30% hydrogen peroxide in the presence of 1 mol% iodide ion at room temperature. This method gives the desired products in high yields without producing any undesirable waste products.

All reagents were purchased from Nacalai Tesque, Wako Pure Chemicals Industry, Kanto Kagaku, Kishida Reagents Chemicals, Tokyo Chemical Indstry, or Aldrich, and used without further purification. Melting points were measured with a Yanaco micro melting point apparatus (MP-J3) and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on JEOL (JNM-EX400) spectrometer as solutions in $CDCl_3$ or D_2O using TMS or the residual solvent peak as an internal standard.

Oxidation of Thiols to Disulfides in EtOAc; General Procedure

To a stirred solution of a thiol (1 mmol) in EtOAc (3 mL) was added NaI (1.5 mg, 0.01 mmol) and 30% H_2O_2 (0.11 ml, 1 mmol) and the mixture was stirred at r.t. for 0.5 h. Sat. aq $Na_2S_2O_3$ (15 mL) was added, and the resulting mixture was extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with brine (15 mL) and dried ($MgSO_4$). The solvent was evaporated, and the residue was purified by silica gel column chromatography (hexane–EtOAc) to afford the pure products.

Oxidation of Thiols to Disulfides in the Absence of a Solvent; General Procedure

To a stirred suspension of a thiol (1 mmol) in H_2O (3 mL) was added NaI (1.5 mg, 0.01 mmol) and 30% H_2O_2 (0.11 mL, 1 mmol) and the mixture was stirred at r.t. for 24 h. Sat. aq $Na_2S_2O_3$ (15 mL) was added, and the resulting mixture was extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with brine (15 mL) and dried ($MgSO_4$). The solvent was evaporated, and the resi-

due was purified by silica gel column chromatography (hexane–EtOAc) to afford the pure products.

Oxidation of L-Cysteine to L-Cystine

To a stirred solution of L-cysteine (606 mg, 5 mmol) in H_2O (10 mL) was added NaI (7.5 mg, 0.05 mmol) and 30% H_2O_2 (0.55 mL, 5 mmol) and the mixture was stirred at r.t. for 0.5 h. The precipitated L-cystine was collected by filtration. The desired L-cystine was obtained as a colorless solid (574 mg, 96%). The NMR data for this compound were identical with those in the literature[8] and with an authentic sample purchased from Kishida Reagents Chemicals; mp 216–220 °C (dec.) [Lit.[9] mp 260–261 °C (dec.)].

^{1}H NMR (D_2O): δ = 3.10 (2 H, dd, *J* = 8.17, 14.76 Hz), 3.30 (2 H, dd, *J* = 3.96, 14.76 Hz), 4.03 (2 H, dd, *J* = 3.96, 8.17 Hz).

Dibenzyl Disulfide

Oxidation of benzyl-1-thiol (0.124 g, 1.0 mmol) following the general procedure gave dibenzyl disulfide (0.118 g, 96%) as colorless crystals; mp 70–71 °C (Lit.[10] mp 70–71 °C).

^{1}H NMR ($CDCl_3$): δ = 3.60 (4 H, s), 7.22–7.35 (10 H, m).

^{13}C NMR ($CDCl_3$): δ = 43.3, 127.4, 128.5, 129.4, 137.4.

Dibutyl Disulfide

Oxidation of butyl-1-thiol (0.090 g, 1.0 mmol) following the general procedure gave dibutyl disulfide (0.089 g, 96%) as a colorless oil. The NMR data of this compound were identical with those in the literature.[1e]

^{1}H NMR ($CDCl_3$): δ = 0.93 (6 H, t, *J* = 7.35 Hz), 1.42 (4 H, sext, *J* = 7.35 Hz), 1.66 (4 H, quint, *J* = 7.35 Hz), 2.69 (4 H, t, *J* = 7.35 Hz).

^{13}C NMR ($CDCl_3$): δ = 13.7, 21.6, 31.3, 38.9.

Didodecyl Disulfide

Oxidation of dodecyl-1-thiol (0.202 g, 1.0 mmol) following the general procedure gave didodecyl disulfide (0.201 g, 97%) as colorless crystals; mp 32 °C (Lit.[4] mp 32 °C).

^{1}H NMR ($CDCl_3$): δ = 0.88 (6 H, t, *J* = 6.59 Hz), 1.23–1.40 (36 H, m), 1.67 (4 H, quint, *J* = 7.38 Hz), 2.68 (4 H, t, *J* = 7.38 Hz).

^{13}C NMR ($CDCl_3$): δ = 14.1, 22.7, 28.5, 29.2, 29.3, 29.5, 29.6, 29.6, 30.1, 31.9, 39.2.

Dicyclohexyl Disulfide

Oxidation of cyclohexylthiol (0.116 g, 1.0 mmol) following the general procedure gave dicyclohexyl disulfide (0.113 g, 97%) as a colorless oil. The NMR data of this compound were identical with those in the literature.[11]

^{1}H NMR ($CDCl_3$): δ = 1.20–1.37 (10 H, m), 1.60–1.63 (2 H, m), 1.77–1.79 (4 H, m), 2.03–2.00 (4 H, m), 2.65–2.72 (2 H, m).

^{13}C NMR ($CDCl_3$): δ = 25.7, 26.1, 30.9, 32.8, 50.0.

Di(*tert*-octyl) Disulfide

Oxidation of *tert*-octylthiol (0.146 g, 1.0 mmol) following the general procedure gave di(*tert*-octyl) disulfide (0.35 g, 28%) as a colorless oil. The NMR data of this compound were identical with an authentic sample purchased from Tokyo Chemical Industry.

^{1}H NMR ($CDCl_3$): δ = 1.03 (18 H, s), 1.38 (12 H, s), 1.66 (4 H, s).

^{13}C NMR ($CDCl_3$): δ = 30.0, 31.8, 32.8, 51.5, 54.6.

Difurfuryl Disulfide

Oxidation of furfurylthiol (0.114 g, 1.0 mmol) following the general procedure gave difurfuryl disulfide (0.113 g, 98%) as a colorless oil. The NMR data of this compound were identical with those in the literature.[11]

^{1}H NMR ($CDCl_3$): δ = 3.69 (4 H, s), 6.22 (2 H, d, *J* = 3.17 Hz), 6.33 (2 H, dd, *J* = 1.95, 2.44 Hz), 7.39 (2 H, dd, *J* = 0.73, 1.95 Hz).

^{13}C NMR ($CDCl_3$): δ = 35.7, 108.9, 110.7, 142.4, 150.2.

***p*-Ditolyl Disulfide**

Oxidation of *p*-tolylthiol (0.124 g, 1.0 mmol) following the general procedure gave *p*-ditolyl disulfide (0.121 g, 99%) as colorless crystals; mp 44–45 °C (Lit.[10] mp 43–44 °C).

^{1}H NMR ($CDCl_3$): δ = 2.31 (6 H, s), 7.10 (4 H, d, *J* = 8.05 Hz), 7.38 (4 H, d, *J* = 8.05 Hz).

^{13}C NMR ($CDCl_3$): δ = 21.0, 128.6, 129.8, 133.9, 137.4.

Bis(4-chlorophenyl) Disulfide

Oxidation of 4-chlorophenylthiol (0.144 g, 1.0 mmol) following the general procedure gave bis(4-chlorophenyl) disulfide (0.132 g, 92%) as colorless crystals; mp 72–73 °C (Lit.[10] mp 71–72 °C).

^{1}H NMR ($CDCl_3$): δ = 7.27 (4 H, d, *J* = 8.54 Hz), 7.40 (4 H, d, *J* = 8.54 Hz).

^{13}C NMR ($CDCl_3$): δ = 129.3, 129.4, 133.7, 135.1.

Bis(4-nitrophenyl) Disulfide

Oxidation of 4-nitrophenylthiol (0.155 g, 1.0 mmol) following the general procedure gave bis(4-nitrophenyl) disulfide (0.136 g, 93%) as brown crystals; mp 188–189 °C (Lit.[12] mp 182 °C).

^{1}H NMR ($CDCl_3$): δ = 7.62 (4 H, d, *J* = 9.02 Hz), 8.20 (4 H, d, *J* = 9.02 Hz).

^{13}C NMR ($CDCl_3$): δ = 124.0, 124.4, 126.4, 144.1.

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References

(1) (a) Uemura, S. In *Comprehensive Organic Synthesis*, Vol. 7; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, **1991**, 757. (b) Aida, T.; Akasaka, T.; Furukawa, N.; Oae, S. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1441. (c) Wu, X.; Reike, R. D.; Zhu, L. *Synth. Commun.* **1996**, *26*, 191. (d) Drabowicz, J.; Mikolajczyk, M. *Synthesis* **1980**, 32. (e) Noureldine, N. A.; Caldwell, M.; Hendry, J.; Lee, D. G. *Synthesis* **1998**, 1587. (f) Tam, J. P.; Wu, C.-R.; Liu, W.; Zhang, J.-W. *J. Am. Chem. Soc.* **1991**, *113*, 6657. (g) Sanz, R.; Aguado, R.; Pedrosa, M. R.; Arnáiz, F. J. *Synthesis* **2002**, 856. (h) Karimi, B.; Hazarkhani, H.; Zareyee, D. *Synthesis* **2002**, 2513.

(2) (a) Nagano, T.; Yoshikawa, K.; Hirobe, M. *Tetrahedron Lett.* **1980**, *21*, 297. (b) Cervilla, A.; Corma, A.; Fornés, V.; Llopis, E.; Palanca, P.; Rey, F.; Ribera, A. *J. Am. Chem. Soc.* **1994**, *116*, 1595. (c) Iranpoor, N.; Zeynizadeh, B. *Synthesis* **1999**, 49. (d) Kirihara, M.; Okubo, K.; Uchiyama, T.; Kato, Y.; Ochiai, Y.; Matsushita, S.; Hatano, A.; Kanamori, K. *Chem. Pharm. Bull.* **2004**, *52*, 625. (e) Arisawa, M.; Sugata, C.; Yamaguchi, M. *Tetrahedron Lett.* **2005**, *46*, 6907.

(3) (a) Price, C. C.; Stacy, G. W. *Org. Synth. Coll. Vol. III*; Wiley: New York, **1955**, 86. (b) Kesavan, V.; Bonnet-Delpon, D.; Bégué, J.-P. *Synthesis* **2000**, 223.

(4) Wallace, T. J. *J. Org. Chem.* **1966**, *31*, 1217.

(5) (a) Behzad, Z. *J. Chem. Research, Synop.* **2002**, 564. (b) Aida, T.; Akasaka, T.; Furukawa, N.; Oae, S. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1441. (c) Drabowicz, J.; Mikołajczyk, M. *Synthesis* **1980**, 32.

(6) (a) Yiannios, C. N.; Karabinos, J. V. *J. Org. Chem.* **1963**, *28*, 3246. (b) Arterburn, J. B.; Perry, M. C.; Nelson, S. L.; Dible, B. R.; Holguin, M. S. *J. Am. Chem. Soc.* **1997**, *119*, 9309.
(7) Relyea, D. I.; Tawney, P. O.; Williams, A. R. *J. Org. Chem.* **1962**, *27*, 477.
(8) Shih, H. *J. Org. Chem.* **1993**, *58*, 3003.
(9) *The Merck Index, 13th ed.*; Merck & Co., Inc.,: Rahway, **2001**.
(10) Huang, X.; Chan, C.-C. *Synthesis* **1982**, 1091.
(11) Choi, J.; Yun, N. M. *J. Org. Chem.* **1995**, *60*, 3266.
(12) Lide, D. R. *CRC Handbook of Chemistry and Physics*, 74th ed.; CRC Press: Ann Arbor, **1993**.