A Simple Procedure for the Oxidation of Thiols to Disulphides by Means of Bromine/Aqueous Potassium Hydrogen Carbonate in a Two-Phase System[1]

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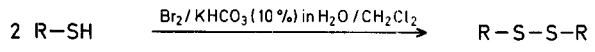
The conversion of thiols to the corresponding disulphides (oxidative *S*–*S* coupling) is of interest both from a biological[2] and a practical point of view. Under biological conditions, this process was found to occur in the presence of oxidants such as flavins, cytochromes, and dehydroascorbic acid[3]. In the laboratory, a wide range of oxidants may be used to accomplish the thiol-disulphide conversion; for instance, redox dyes[4], nitro compounds[5], diazo compounds[6], sulphoxides[7], and halogens[8,9] can oxidize thiols to disulphides. Recently, the use of 2-polyvinylpyridine/bromine complex as a useful reagent for oxidizing thiols to disulphides was reported[10].

In the course of our studies[11] on the oxidation of organic sulphur compounds it was found that the oxidation of thiols **1** to the corresponding disulphides **2** occurs instantaneously at room temperature when bromine/aqueous potassium hydrogen carbonate is used under two-phase conditions.



1 **2**

A typical procedure consists of the addition of bromine to a well-stirred heterogenic mixture of the thiol **1** in dichloromethane and 10% aqueous solution of potassium hydrogen carbonate. The results listed in the Table show that this procedure may be applied to alkanethiols, arylalkanthiols, and arenethiols. In all cases, the disulphides **2** are obtained in almost quantitative yield. It should be noted that T.L.C. analysis indicated the formation of only one product. It is also worth mentioning that in the oxidation of benzylmercaptan **(1d)** under the conditions described above, further bromination of the disulphide **2d** formed was not observed.

The general utility of this oxidation method is further shown by its successful application to thiols containing other functional groups. Thus, for example, treatment of 2-mercaptoethanol **(1h)** with bromine/potassium hydrogen carbonate under two-phase conditions afforded bis[2-hydroxyethyl] disulphide **2h** in 74% yield after distillation.

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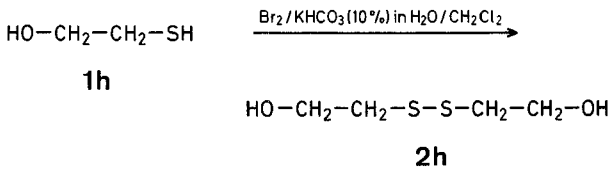
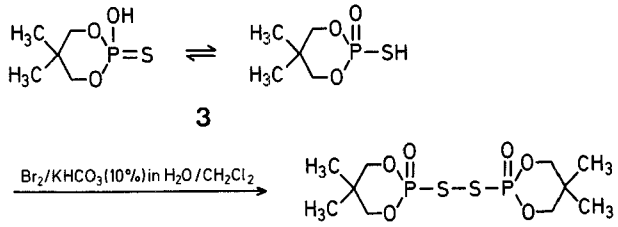


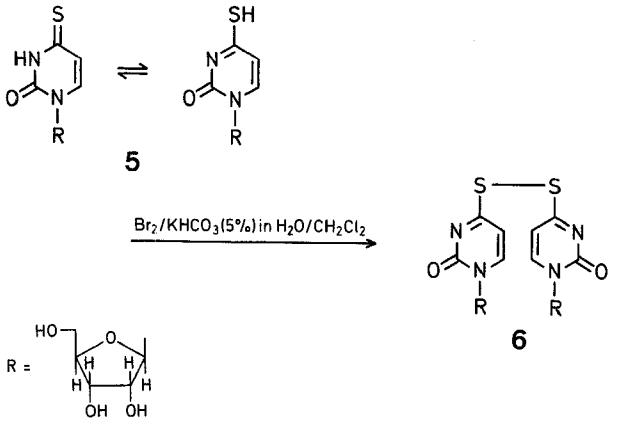
1h **2h**

Similarly, oxidation of the cyclic thioacid **3** was achieved under the same conditions to give the disulphide **4** in 89% yield.



3 **4**

Finally, our oxidation procedure was successfully applied to the oxidative *S*—*S* coupling of 4-thiouridine (**5**) which is a minor component of transfer-ribonucleic acids (t-RNA)[12]. The reaction of bromine with **5** proceeds fast and affords the corresponding disulphide **6** in 92% yield.



5 **6**

It is interesting to note that no degradation of the sensitive ribose moiety was observed under the reaction conditions employed.

In summary, the high yields obtained under mild conditions, the applicability to functionally substituted thiols, the use of cheap and common laboratory reagents, the absence of side reactions, and the simple work-up make the present procedure useful for the oxidative *S*—*S* coupling of thiols to symmetrical disulphides.

Oxidation of Thiols 1 to Disulphides 2; General Procedure:
A round bottom flask is charged with dichloromethane (20 ml), the thiol **1** (20 mmol), and 10% aqueous potassium hydrogen carbonate (20 ml). The flask is immersed in a water bath and a solution of bromine (1.6 g, 10 mmol) is added slowly to the well-stirred mixture. During the addition of bromine, the colour disappears quickly. After addition is complete, the organic phase is separated and the aqueous phase extracted with dichloromethane (20 ml). The organic phases are combined and dried with magnesium sulphate. Evaporation of the solvent gives virtually pure **2** (according to ^{1}H-N.M.R. and T.L.C. analysis.

Bis[2-hydroxyethyl] Disulphide (2h):
2-Mercaptoethanol (**1h**; 3.12 g, 40 mmol) is oxidized under the conditions described above. The crude product **2h** is purified by distillation in vacuo; yield: 2.26 g (74%); b.p. 150–152 °C/0.01 torr (Ref. [10], b.p. 160–162 °C/0.1 torr).

M.S.: $m/e = 154$ (M^+, 70%); 110 (18); 92 (100).

Bis[5,5-dimethyl-2-oxo-P^V-1,3,2-dioxaphosphorinan-2-yl] Disulphide (4):
5,5-Dimethyl-2-hydroxy-2-thioxo-*P*^{V}-1,3,2-dioxaphosphorinan (**3**; 1.82 g, 10 mmol) is oxidized as described above; yield: 1.61 g (89%); m.p. 139–141 °C. The product is pure as evidenced by ^{31}P-N.M.R. and T.L.C. analysis (silica gel, 10:1 benzene/methanol as eluent).

$C_{10}H_{20}O_6P_2S_2$	calc.	C 33.14	H 5.56	S 17.69
(362.2)	found	33.50	5.80	17.66

^{31}P-N.M.R. ($CHCl_3$/TMS): $\delta = +12.3$ ppm.

Disulphide 6 from 4-Thiouridine (5):
A solution of bromine (8 mg) in dichloromethane (1 ml) is added to a well-stirred mixture of 4-thiouridine (**5**; 25.9 mg, 0.1 mmol), dichloromethane (120 ml), and 5% aqueous potassium hydrogen carbonate (20 ml). The bromine colour disappears soon. The water layer is separated and evaporated under reduced pressure. The residue is extracted with methanol (3 × 20 ml) and the extract evaporated in vacuo to afford **6**; yield: 23 mg (92%); m.p. > 270 °C (dec.) (Ref. [19]).

U.V. (ethanol): $\lambda_{max} = 320$ ($\varepsilon = 29850$); 261 (6500); $\lambda_{min} = 280$ nm (5400); cf. Ref. [19].

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Table. Disulphides (**2**) from Thiols (**1**)[a]

2	R	Yield[b] [%]	m.p. or b.p. found	m.p. or b.p. reported	n_D^{20} found	n_D^{20} reported
a	C_2H_5	95	b.p. 56–58 °C/25 torr	b.p. 154 °C/760[8,9]	1.5073	1.5066[9]
b	*i*-C_3H_7	92	b.p. 68–69 °C/2 torr	b.p. 174 °C/760 torr[8,9]	1.4905	1.4909[8,9]
c	*n*-C_4H_9	96	b.p. 114–115 °C/18 torr	b.p. 115 °C/17 torr[13]	1.4923	1.4926[14]
d	C_6H_5—CH_2—	98	m.p. 72 °C (m.m.p. 71–72 °C)	m.p. 71 °C[15]		
e	C_6H_5	100	m.p. 61–62 °C (m.m.p. 61–62 °C)	m.p. 61 °C/16		
f	4-H_3C—C_6H_4—	100	m.p. 45–46 °C (m.m.p. 46–47 °C)	m.p. 46 °C[17]		
g	4-H_3CO—C_6H_4—	97	m.p. 42–44 °C (m.m.p. 43–45 °C)	m.p. 45 °C[18]		

[a] The reaction was carried out with 40 mmol of alkanethiol or 20 mmol of arenethiol.
[b] Yield of pure product (purity control by ^{1}H-N.M.R. and T.L.C).

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