Simple conversion of thiols to disulfides in EtOH under ambient aerobic conditions without using any catalyst or additive

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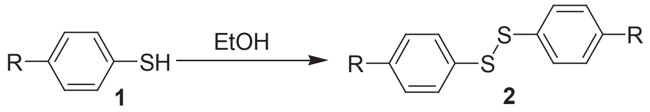
EtOH was found to be an excellent medium for the aerobic S–S coupling reactions of various alkyl and aryl thiols. A series of useful disulfides RSSR have been synthesised in good to excellent yields without using any additional catalyst, oxidant or additive. Moreover, most products could be obtained by simply removing the solvent after completion of the reaction. Satisfactory results were obtained for both mg- and g-scale reactions.

Keywords: catalyst-free, aerobic, thiol coupling, disulfides, scale-up synthesis

The chemistry of disulfides is a topic of high interest owing to their usefulness in the chemical industry as well as for laboratory synthesis. The most notable application of disulfides is acting as operationally friendly thiolating reagents as well precursors for sulfones/sulfoxides synthesis. Although the synthesis of disulfides using oxidative coupling of thiols has been known as a classical protocol, the development of cleaner, simpler and scalable catalytic methods to synthesise these products is still of great interest.

We have very recently reported the successful autoxidation of thiols RSH to disulfides RSSR using ethyl lactate as a solvent without the addition of catalyst or any additive.[1] We have now found that the reaction can be carried out more efficiently and in good to excellent yields in the simple solvent, ethanol, again without the addition of catalyst or any additive. Moreover, the isolation of products merely requires evaporation of this low-boiling solvent. We here describe our results which include the conversion of aryl, heteroaryl and alkyl thiols to disulfides on both the milligram and gram scale (Scheme 1).



Scheme 1

Results and discussion

When thiophenol **1a** (1 mM) was dissolved in EtOH (2 mL) at 60 °C and stirred for 12 h without using any additional reagent, diphenyl disulfide **2a** was obtained in 77% yield. This interesting result prompted us to further optimise the reaction conditions and the results are shown in Table 1. Performing the reaction at 45 °C or at room temperature gave similar yields of product (entries 1–3, Table 1; TLC analysis was used to monitor the reactions). Shortening the reaction times from 12 to 10, 8, 6, 4 and 2 h revealed that 4 h was optimal by giving a yield of 83% (entries 4–8, Table 1). When the amount of EtOH was reduced from 2 mL to 1.0 mL, the yield was similar, but the yield dropped off when the volume was reduced to 0.5 mL (entries 9–10, Table 1).

Table 1 Optimisation of reaction conditions for the conversion of thiophenol **1a** to diphenyl disulfide **2a** (Scheme 1; R=H)[a]

Entry	T/°C	t/h	Yield/%[b]
1	60	12	77
2	45	12	76
3	25	12	78
4	25	10	75
5	25	8	79
6	25	6	80
7	25	4	83
8	25	2	62
9[c]	25	4	84
10[d]	25	4	71

[a]Reaction conditions: **1a** (1 mmol) in EtOH (1 mL) was stirred at room temperature in the air.

[b]Yield of isolated product **2a**.

[c]EtOH was 1.0 mL; [d]EtOH was 0.5 mL.

Using the optimised conditions of stirring a solution of thiols **1** (1 mM) in EtOH (1 mL) for 4 h, a series of aryl, heteroaryl and alkyl thiols were investigated and the results are shown in Table 2. As can be seen, the yields of the dialkyl and diaryl disulfides are all in the good to excellent range of 81–94% (entries 2–10, Table 2), so the method shows wide applicability. Only the naphth-2-yl and pyridine-2-yl thiols gave slightly lower yields in the range 75–78% (entries 11 and 12, Table 2). All the products are known and have been confirmed by comparing their ^{1}H NMR spectra as well as melting points (for solids) with literature results.

We also investigated whether the method could be scaled up 10-fold. We chose three thiophenols for experiments on the 10 mM scale. By simply stirring each of the compounds in the open air in EtOH (10 mL) for 6 h, the conversion of thiophenol **1a**, 4-methylthiophenol **1b** and 4-bromothiophenol **1d** to the

Table 2 EtOH-mediated catalyst- and additive-free conversion of thiols **1** to disulfides **2** (Scheme 1)[a]

Entry	R	Product	Yield/%[b]	M.p./°C)[lit.]
1	Ph	**2a**	84	59–60 [58–60][1]
2	4-MeC$_6$H$_4$	**2b**	86	Pale yellow liquid[2]
3	4-FC$_6$H$_4$	**2c**	81	Pale yellow liquid[3]
4	4-BrC$_6$H$_4$	**2d**	94	91–92 [94–96][1]
5	4-*i*-PrC$_6$H$_4$	**2e**	90	Pale yellow liquid[4]
6	Benzyl	**2f**	92	61–62 [63–65][1]
7	Octyl	**2g**	83	Colourless liquid[5]
8	2-MeC$_6$H$_4$	**2h**	85	Yellow liquid[6]
9	3-MeC$_6$H$_4$	**2i**	82	Yellow liquid[7]
10[c]	2-ClC$_6$H$_4$	**2j**	83	82–84 [85–87][1]
11[c]	Napth-2-yl	**2k**	78	135–136 [355–137][1]
12[c]	Pyridin-2-yl	**2l**	75	Yellow liquid[2]

[a]General conditions: **1a** (1 mmol) in alcohol (1 mL), was stirred at room temperature in the air for 4 h.

[b]Yield of isolated product.

[c]The products were purified by silica gel column chromatography.

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corresponding diaryl disulfides was achieved in excellent yields of 80, 91 and 94%, respectively. These very satisfactory results illustrated the great potential of this procedure in large-scale synthesis.

Experimental

All chemicals were obtained from commercial sources and used without further purification. ^{1}H NMR spectra were recorded on a Bruker Avance 400 apparatus (400 MHz) in $CDCl_3$. Chemical shifts were reported in ppm with TMS as internal standard. Melting points were determined using a X-4A apparatus and were uncorrected.

Thiol coupling reactions for the synthesis of disulfides

General procedure (1mM scale): In a 25 mL round bottom flask, a thiol (**1**; 1.0 mmol) was dissolved in EtOH (1 mL) and the mixture was stirred in the open atmosphere for 4 h (completion of reaction was confirmed by TLC). Then the mixture in the flask was evaporated *in vacuo*. The residue was either directly dried to give pure products **2a–i** or subjected to silica gel column chromatography using petroleum ether as eluent to give pure products **2j–l** (see Table 2).

General procedure (10 mM scale): In a 50 mL round bottom flask, a thiol (**1a**, **1b** or **1d**; 10.0 mmol) was dissolved in EtOH (10 mL) and the mixture was stirred in the open atmosphere for 6 h (progress of reaction was followed by TLC). Evaporation of solvent provided the corresponding pure disulfides **2a**, **2b** and **2d**.

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