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DIETHYLAMINE-CATALYZED DIMERIZATION OF THIOLS: AN INEXPENSIVE AND GREEN METHOD FOR THE SYNTHESIS OF HOMODISULFIDES UNDER AQUEOUS CONDITIONS

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Under H_2O / Et_2NH / atmospheric oxygen conditions, thiols are converted to their respective homodisulfides within a few hours. The process is conducted at room temperature for quantitative dimerization of aromatic, benzylic, and aliphatic thiols without the use of any extra additive.

Keywords: Aqueous conditions; disulfides; oxidation; thiols

The disulfide moiety is found in many biologically important structures[1] and is considered as a useful synthon for certain organic synthetic transformations such as sulfenylation of anions,[2] protection of thiols,[3] and oxidation of organic functional groups.[4] Homodisulfides are generally synthesized via oxidative coupling of their corresponding thiols.[5] Many procedures are offered for this conversion including using halogen-containing reagents,[6] metal ions,[7] iodine,[8] chromium-based oxidants,[9] permanganate-based reagents,[10] enzymatic procedures,[11] electrochemical methods,[12] hydrogen peroxide,[13] ammonium persulfate,[14] and nanoparticles.[15] However, many of these methods involve overoxidation of products, require difficult workup or isolation procedures, need stoichiometric amounts of expensive and/or toxic reagents, and use strong oxidizing agents. As a result, development of simple and straightforward environmentally friendly protocols capable of smoothly transfering thiols to disulfides is of great interest.

The most inexpensive and safe source of oxidation is molecular oxygen, which is used in several procedures for transformation of thiols to disulfides.[16] However, in the available methods, use of solvents, catalysts, or additives is required. In the framework of our investigations on the development of new environmentally benign synthetic procedures,[17] we recently published a few articles on the use of aqueous media for smooth transformation of functional groups.[18] In the present work, we reveal a very straightforward and inexpensive procedure for rapid and efficient

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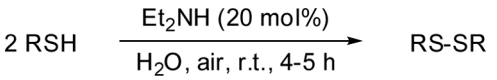


Scheme 1.

conversion of thiols to their respective homodisulfides using ambient air under H_2O/Et_2NH conditions (Scheme 1). To our knowledge, this is the most inexpensive and environmentally friendly procedure offered so far for conversion of thiols to disulfides.

Table 1 highlights the results obtained from the experiments primarily conducted to optimize the reaction conditions for oxidative coupling of benzenethiol. Under atmospheric air pressure and at ambient temperature, use of 20 mol% of Et_2NH in 1 mL of tap water gave optimized conditions for converting the starting thiol to its respective disulfide **1a** after 5 h (entries 1–4). Use of lesser amounts of the amine (entry 5) or water (entries 6 and 7) decreased the yield of **1a** after the same time period, illustrating their crucial roles in the reaction. Alternatively, omission of either Et_2NH (entry 8) or H_2O (entry 9) suppressed the reaction significantly. Even under flow of O_2 gas, product **1a** was formed only in 30% yield under nonaqueous conditions (entry 10). Other secondary amines (entries 11–14) and hexylamine (entry 15) more or less behaved equally well, while tertiary amines were unsuccessful in inducing the same reaction even in longer time periods (entries 16 and 17), perhaps because of their lower solubility in water comparing to secondary amines.[19]

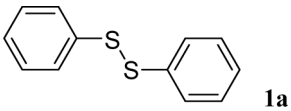
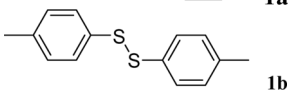
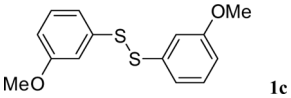
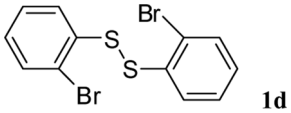
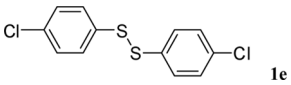
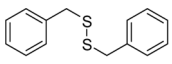
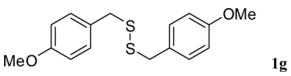
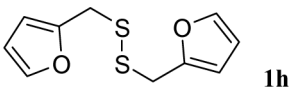
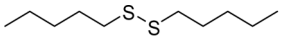
We next used the optimized conditions to convert various thiols to their respective homodisulfides as shown in Table 2. Benzenethiol (entry 1) and its electron-releasing and electron-withdrawing derivatives (entries 2–5) all gave good

Table 1. Optimization of the conditions for oxidation of benzenethiol

Entry	Amine	Amine (mol%)	Medium	Yield (%)[a]
1	Et_2NH	Excess	H_2O (1 mL)	99
2	Et_2NH	100	H_2O (1 mL)	99
3	Et_2NH	50	H_2O (1 mL)	99
4	Et_2NH	20	H_2O (1 mL)	99
5	Et_2NH	10	H_2O (1 mL)	73
6	Et_2NH	20	H_2O (0.5 mL)	80
7	Et_2NH	20	H_2O (0.2 mL)	70
8	—		H_2O (1 mL)	0
9	Et_2NH	100	—	18
10	Et_2NH	100	—	30[b]
11	Pyrrolidine	20	H_2O (1 mL)	84
12	Piperidine	20	H_2O (1 mL)	93
13	Morpholine	20	H_2O (1 mL)	86
14	Diisopropylamine	20	H_2O (1 mL)	94
15	Hexylamine	20	H_2O (1 mL)	95
16	Triethylamine	20	H_2O (1 mL)	5
17	Pyridine	20	H_2O (1 mL)	16

[a]GC yields.
[b]Under O_2 bubbling conditions.

Table 2. H_2O/Et_2NH-mediated oxidation of thiols

Entry	Thiol	Product	Yield (%)[a]
1	C_6H_5SH	 **1a**	99
2	(4-Me)C_6H_4SH	 **1b**	96
3	(3-MeO)C_6H_4SH	 **1c**	95
4	(2-Br)C_6H_4SH	 **1d**	97
5	(4-Cl)C_6H_4SH	 **1e**	95
6	$C_6H_5CH_2SH$	 **1f**	96
7	(4-MeO)$C_6H_4CH_2SH$	 **1g**	94
8	2-furylCH_2SH	 **1h**	97
9	$Me(CH_2)_3CH_2SH$	 **1i**	93

[a]Isolated yields.

yields of products **1a**–**e** within 5 h. Benzylic thiols (entries 6–8) were also converted efficiently to products **1f**–**h** after the same time under the conditions. To examine the aliphatic thiols, pentane-1-thiol was subjected to oxidative dimerization, giving **1i** in 93% yield after 4 h (entry 9). All reactions proceeded rapidly and efficiently at room temperature and under atmospheric pressure of the ambient air, giving their respective single disulfides. Products were identified based on the comparison of their spectral data with those available in the literature.[6a–c,7a,15,20,21]

Based on these observations, a simplified mechanistic pathway is proposed through which the starting thiol is first deprotonated in aqueous Et_2NH medium and then oxidized by atmospheric oxygen to its respective radical. The radicals are subsequently dimerized to form the disulfide products (Fig. 1).

In summary, a very convenient and rapid procedure for conversion of thiols to homodisulfides is offered. Besides the starting thiol and tap water, the only required additive for the reaction to proceed is substoichiometic amounts of Et_2NH. As a consequence, the method is very inexpensive, environmentally safe, and straightforward. These features make the method an interesting addition to the present

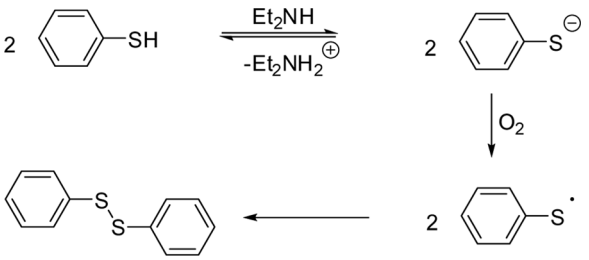


Figure 1. Suggested mechanistic overview of the reactions.

Table 3. H_2O/Et_2NH-mediated oxidation of thiols in comparison with other methods

Conditions	Reaction medium	Yield (%)
Et_2NH[a]	H_2O	99
Et_3N/ultrasound[20]	DMF	97
TMSCl[6b]	DMSO	90
Al_2O_3/KF/MW (heat)[22]	–	73
SO_2Cl_2[6c]	CH_2Cl_2	98
CSF/celite/O_2[7a]	MeCN	78
VO(acac)$_2$/*t*-BuOOH/-15 °C[7b]	CH_2Cl_2	92
HNO_3/0 °C[23]	CH_2Cl_2	87
H_2O_2[13]	$(CF_3)_2CHOH$	99

[a]This work.

literature archive. We can reach a better conclusion by comparing the present procedure with some other available methods as reflected in Table 3.

EXPERIMENTAL

Reactions were monitored by thin-layer chromatography (TLC) using silica-gel-coated plates and ethyl acetate / hexane solutions as the mobile phase. NMR spectra were obtained on a Bruker Ultra Shield (500-MHz) instrument as $CDCl_3$ solutions, and the chemical shifts are expressed as δ units with Me_4Si as the internal standard. All reagents were purchased from commercial sources and were freshly used after being purified by standard procedures. All products are known compounds.

Typical Procedure

A thiol (2 mmol) was added to a homogeneous mixture of Et_2NH (0.4 mmol, 20 mol%) and water (1 mL), and the mixture was stirred under a fume hood for 5 h at ambient atmosphere and room temperature. The course of the reaction was monitored by TLC. The reaction mixture was diluted by Et_2O (5 mL) and extracted by a saturated $NaHCO_3$ (5 mL) and brine (5 mL) solution. The organic layer was dried over Na_2SO_4, and the volatile portion was removed under reduced pressure.

The residue was purified by column chromatography using silica gel and a EtOAc/hexane (1:1) solution, if necessary.

Selected NMR Spectral Data

1,2-Di-4-tolyldisulfane (1b).[15] ^{1}H NMR ($CDCl_3$) δ 2.41 (s, 6H), 7.19 (d, $J = 7.9$ Hz, 4H), 7.49 (d, $J = 7.9$ Hz, 4H); ^{13}C NMR ($CDCl_3$): δ 43.2, 114.4, 129.9, 131.0, 159.5.

1,2-Bis(3-methoxyphenyl)disulfane (1c).[20] ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 6H), 6.80–6.82 (m, 2H), 7.12–7.14 (m, 4H), 7.25 (dd, $J = 7.7$, 8 Hz, 2H);^{13}C NMR ($CDCl_3$): δ 55.7, 113.1, 113.6, 120.1, 130.4, 138.8, 160.5.

1,2-Bis(2-bromophenyl)disulfane (1d).[20] ^{1}H NMR ($CDCl_3$) δ 7.12 (ddd, $J = 1.5$, 7.8, 8 Hz, 2H), 7.30 (ddd, $J = 1$, 7.5, 8 Hz, 2H), 7.56–7.59 (m, 4H), 7.24–7.27 (q, 2H);^{13}C NMR ($CDCl_3$): δ 121.6, 127.5, 128.4, 128.7, 133.4, 136.6.

1,2-Dibenzyldisulfane (1f).[6c] ^{1}H NMR ($CDCl_3$) δ 3.69 (s, 4H), 7.32–7.37 (m, 6H), 7.39–7.42 (m, 4H);^{13}C NMR ($CDCl_3$): δ 43.8, 127.9, 129.0, 129.9, 137.9.

1,2-Dipentyldisulfane (1i).[7a] ^{1}H NMR ($CDCl_3$) δ 0.91 (t, $J = 7$ Hz, 6H), 1.36–1.42 (m, 8H), 1.70–1.73 (m, 4H), 2.72 (t, $J = 7.5$ Hz, 4H);^{13}C NMR ($CDCl_3$): δ 14.4, 22.7, 29.3, 31.1, 39.6.

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