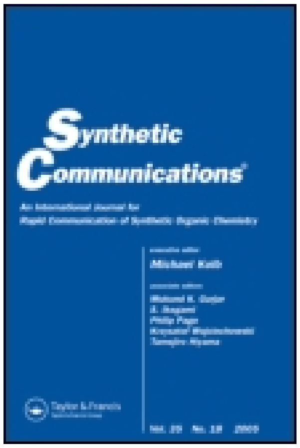

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TETRABUTYLAMMONIUM PEROXYDISULFATE IN ORGANIC SYNTHESIS. XII.[1] A CONVENIENT AND PRACTICAL PROCEDURE FOR THE SELECTIVE OXIDATION OF THIOLS TO DISULFIDES WITH TETRABUTYLAMMONIUM PEROXYDISULFATE UNDER SOLVENT-FREE CONDITIONS

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ABSTRACT

An efficient method for the oxidative coupling of thiols to their corresponding disulfide by $(n\text{-Bu}_4\text{N}_2)\text{S}_2\text{O}_8$ in high yields under solvent-free conditions is described. The reaction was applicable to a variety of thiols with high chemoselectivity.

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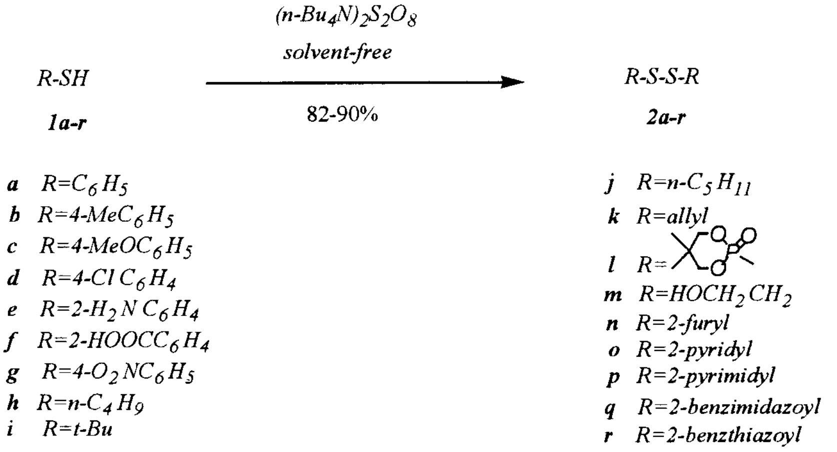
Selective oxidation of thiols to disulfides is of practical importance both in biochemistry[2] and in synthetic chemistry.[3] Disulfides are also important intermediates with a lot of applications in organic synthesis. For example, they serve as precursors for the synthesis of dithiin derivatives,[4] 4*H*-1,4-benzothiazines[5] and thiocarbonyl compounds[6] etc. Since thiols are among functional groups which can be easily over-oxidized, a variety of chemical oxidation (O_2,[7] $Br_2/KHCO_3$,[8] I_2/HI,[9] $FeCl_3/Bu_3SnOMe$,[10] $FeCl_3/NaI$,[11] $KMnO_4/CuSO_4$,[12] $H_2O_2/HFIP$,[13] $Ca(OCl_2)_2$,[14] Sm/BiC_{13},[15] TTCPP,[16] $Zn(BiO_3)_2$,[17] $Cu(NO_3)_2$,[18] *bis* [benzyltriethyl] ammonium dichromate[19] and benzyltriphenyl phosphonium dichromate,[20] etc), electrochemical oxidation[21] and enzymatic (horseradish peroxidase or mushroom tyrosinase[22] and Baker's yeast[23]) methods have been developed for the controlled oxidative coupling of thiols to disulfides. However, most of the existing methods use toxic metal ions and solvents which are detrimental to the environment, lack the general applicability to thiol substrates bearing alkyl, aryl, and heterocyclic moieties, isolation and form over oxidation products leading to lower yield. As a result, there is still a need for the development of general, efficient, and eco-friendly methodology to synthesize aliphatic, aromatic, and heterocyclic disulfides from the corresponding thiols under mild reaction conditions. In recent years, the use of solvent-free synthesis has been proven to present many advantages over conventional solution procedures in organic synthesis.[24] In the light of ever increasing environmental concern about today's chemical research, attempts are on to perform the organic reaction in the solid state. During the course of our systematic study on oxidation of organic compounds with tetrabutylammonium peroxydisulfate [$(n\text{-}Bu_4N_2)S_2O_8$],[25] we report here a facile and selective oxidation of thiols to disulfide using [$(n\text{-}Bu_4N_2)S_2O_8$] under solvent-free conditions as displayed in Sch. 1.

The feasibility of the present oxidation of thiols was first examined using benzenethiol **1a** as a model substrate. Thus, **1a** was thoroughly mixed with 1.1 equivalents of $(n\text{-}Bu_4N)_2S_2O_8$ in a mortar with a pestle and in an ambient air environment at room temperature and the desirable coupling product **2a** was obtained in 87% yield within 5 min (Entry 1). It is noteworthy that the oxidation did not proceed to completion even after prolonged hours of reaction (1.5 h) when less than 1.1 equivalents of the oxidant was used.

With the first successful result in hand, oxidative coupling reactions of other thiols (**1b–r**) with $(n\text{-}Bu_4N)_2S_2O_8$ were carried out under similar reaction conditions. The results obtained are presented in Table 1. As shown in the Table 1, aliphatic, aromatic, and the heterocyclic thiols were oxidized to the corresponding disulfides in substantially quantitative yields with very



Scheme 1.

short times (4–6 min). Electronic and/or steric variation of the thiols has no effect on the efficiency of either the oxidation reaction rate or yields of the reaction. Other oxidizable functional groups such as amino (Entry 5), hydroxy (Entry 13), and C, C double bonds (Entry 11) present in some of the substrates tested were found to be tolerated under the present protocol. It should also be noted was that under the present reaction conditions, purity of the product was >99% in all cases and no other over-oxidized byproducts were detected on GC and by ^{1}H NMR spectroscopy, even when the reactions were carried out with an excess of the oxidant.

In conclusion, the oxidation of thiols using $(n\text{-Bu}_4\text{N})_2\text{S}_2\text{O}_8$ under solvent-free conditions provides a very rapid, general, and environmentally benign procedure for the high-yielding preparation of a variety of disulfides that may find useful, practical applications in organic synthesis.

EXPERIMENTAL

All melting points were determined on a WRS-1 digital melting point apparatus, and are uncorrected. IR spectra were recorded on a Nicolet FI-IR 360 spectrometer. ^{1}H NMR spectra were measured on a Brucker AC-80 or DPX 300 spectrometer using $CDCl_3$ as solvent and TMS as an internal standard. TLC was performed on Silica Gel 60 F_{254} purchased from Qing Dao Marine Chemical Company (China). The purity determination of products was accomplished by GC on a Shimadzu GC-14A instrument.

Table 1. Oxidation of Thiols **1a–r** to Disulfides **2a–r** with $(n\text{-Bu}_4\text{N})_2\text{S}_2\text{O}_8$ Under Solvent-Free Conditions

Entry	Thiol	Reaction Time (min)	Product[a]	Yield[b] (%)	M.P. (°) or B.P. (°)/Torr Found	M.P. (°) or B.P. (°)/Torr Reported
1	**1a**	5	**2a**	87	61–62	58–60[13]
2	**1b**	6	**2b**	88	45–47	45–46[11]
3	**1c**	5	**2c**	86	44–45	42–44[8]
4	**1d**	5	**2d**	82	73–74	72–73[19]
5	**1e**	6	**2e**	88	79–81	80[20]
6	**1f**	5	**2f**	90	288–290	286[20]
7	**1g**	5	**2g**	88	184–185	184–186[20]
8	**1h**	6	**2h**	88	113–115/18	115/17[26]
9	**1i**	5	**2i**	86	111–114/15	197–200[20]
10	**1j**	5	**2j**	86	90–92/1	89–91/1[27]
11	**1k**	5	**2k**	90	137–198/760	139/760[28]
12	**1l**	4	**2l**	87	140–141	139–141[8]
13	**1m**	6	**2m**	88	140–141/1	150–152/0.01[8]
14	**1n**	6	**2n**	86	120–121/1	118–120/0.8[20]
15	**1o**	5	**2o**	85	56–58	54–57[17]
16	**1p**	5	**2p**	83	144–146	141–145[17]
17	**1q**	5	**2q**	86	199–201	200–201[20]
18	**1r**	6	**2r**	87	181–182	183–184[11]

[a] All products were characterized by IR, ^{1}H NMR, MS, and comparison of the TLC, m.p. with those of authentic samples.

[b] Yields of isolated pure product.

Mass spectra were measured on HP-5989A spectrometer by direct inlet at 70 eV. Thiols were obtained from Joint Venture Zhejiang Shou & Fu Chemical Company (China) or Aldrich Chemical Company and are used without further purification. $(n\text{-Bu}_4\text{N})_2\text{S}_2\text{O}_8$ was prepared according the literature procedure.[29]

Typical procedure for the oxidation of thiols benzenethiol (1a) to diphenyl disulfide (2a): A mixture of benzenethiol (**1a**) (10 mmol, 1.1 g) and $(n\text{-Bu}_4\text{N})_2\text{S}_2\text{O}_8$ (5.5 mmol, 3.73 g) was ground thoroughly in a mortar and pestle in for 5 min at room temperature until the reaction was complete by GC monitoring. The product was extracted with Et_2O (4 × 35 mL). The combined Et_2O layers were washed with brine (315 mL), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give crude product, which was recrystallized from EtOH to give pure **2a** (1.6 g, 87%) as colorless crystals; m.p. 61–62°C (lit.[13] 58–60°C), IR (KBr): $\nu = 3048, 1570, 1473, 1435, 685, 469\,\mathrm{cm}^{-1}$. ^{1}H NMR: $\delta = 7.45$–7.50 (m, 4H), 7.22–7.39 (m, 6H).

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