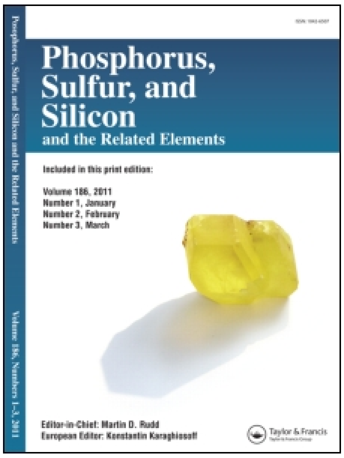


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Oxidation of Thiols to the Corresponding Symmetric Disulfides with Benzyltriphenylphosphonium Peroxodisulfate (BTPPD) Under Nonaqueous Conditions

Abdol R. Hajipour[a][b]; Arnold E. Ruoho[a]
[a] Medical School, University of Wisconsin, Madison, Wisconsin, USA [b] Isfahan University of Technology, Isfahan, Iran

To cite this Article Hajipour, Abdol R. and Ruoho, Arnold E.(2003) 'Oxidation of Thiols to the Corresponding Symmetric Disulfides with Benzyltriphenylphosphonium Peroxodisulfate (BTPPD) Under Nonaqueous Conditions', Phosphorus, Sulfur, and Silicon and the Related Elements, 178: 6, 1277 — 1281

To link to this Article: DOI: 10.1080/10426500307894

URL: http://dx.doi.org/10.1080/10426500307894

Phosphorus, Sulfur, and Silicon, 178:1277–1281, 2003
Copyright © Taylor & Francis Inc.
ISSN: 1042-6507 print
DOI: 10.1080/10426500390200567

OXIDATION OF THIOLS TO THE CORRESPONDING SYMMETRIC DISULFIDES WITH BENZYLTRIPHENYLPHOSPHONIUM PEROXODISULFATE (BTPPD) UNDER NONAQUEOUS CONDITIONS

Abdol R. Hajipour[a,b] *and Arnold E. Ruoho*[a]
University of Wisconsin, Medical School, Madison, Wisconsin, USA;[a] *and Isfahan University of Technology, Isfahan Iran*[b]

(Received October 29, 2002; accepted November 18, 2002)

This article describes the preparation of benzyltriphenylphosphonium peroxodisulfate (BTPPD), an efficient and mild reagent for oxidation of a variety of aromatic and aliphatic thiols to the corresponding disulfides in refluxing acetonitrile. The experimental procedure is simple and the products are easily isolated in excellent yields.

Keywords: Disulfides; oxidation; peroxodisulfate; thiols

Selective oxidative coupling of thiols to disulfides is of interest from both a biological and a synthetic point of view.[1–3] Since thiols are among functional groups, which can be over oxidized, extensive research has been performed to control their oxidation.[4–9] Most of the existing methods involve the use of metal catalysts or reagents like halogens and always suffer from metal ions and solvents that are toxic in nature. The oxidation of thiols **2** to disulfides **3** is a characteristic reaction, and further oxidation to disulfide S-oxides (thiosulfinates), 1,1-dioxides (thiosulfonates), and sulfonic acids are possible. Weak S—S bonds in these compounds impart high reactivity[10] and in natural products these moieties and related cyclic analogues are associated with interesting biological activity and DNA-cleaving properties.[11–12]

We gratefully acknowledge the funding support received for this project from the Isfahan University of Technology (IUT), IR Iran (A.R.H.) and Grant GM 33138 (A.E.R.) from the National Institutes of Health, USA.

Address correspondence to Abdol R. Hajipour, Department of Pharmacology, University of Wisconsin, Medical School, 1300 University Ave., Madison, WI 53706-1532. E-mail: haji@cc.iut.ac.ir

RESULTS AND DISCUSSION

In connection with our ongoing program to introduce new reagents for oxidation of organic compounds under mild conditions,[13–14] we report on the preparation of benzyltriphenylphosphonium peroxodisulfate **1** and the application of this inexpensive and mild reagent for oxidative coupling of a variety of aliphatic and aromatic thiols and aliphatic dithiols to their corresponding acyclic and cyclic disulfides. This reagent is prepared readily by the dropwise addition of $Na_2S_2O_8$ to an aqueous solution of benzyltriphenylphosphonium chloride at room temperature. Filtration and drying of the precipitate produced a white powder which could be stored for months without losing its oxidizing ability.This reagent is quite soluble in methylene chloride, chloroform, acetone, THF, DMF, DMSO, and acetonitrile and insoluble in non-polar solvents, such as carbon tetrachloride, n-hexane, and diethyl ether (Scheme 1).

$$\mathbf{2\,PhCH_2P^+Ph_3Cl^- + Na_2S_2O_8 \xrightarrow[20\ min]{H_2O/RT} \underset{1}{(PhCH_2P^+Ph_3)_2S_2O_8^{2-}} + 2NaCl}$$

SCHEME 1

This method is a remarkably effective methodology for oxidizing aliphatic and aromatic thiols to disulfides. This reagent also exhibits a synthetically valuable method for producing cyclic disulfides from dithiols. The oxidation of dithiols results in the formation of cyclic and/or polymers disulfides. The polymers result from intermolecular oxidation, while the cyclic disulfides arise from intramolecular oxidative coupling of dithiols. For example, oxidative coupling of 1,4-benzenedimethanethiol gives only polymeric product (Table I), while 1,3-dithiol gives 70% cyclic disulfides and 30% polymeric products. The butane 1,4-dithiol gives only cyclic disulfides in 98% yields. It was found that further oxidation producing disulfide to S-oxides, 1,1-dioxides, and sulfonic acid did not occur. A series of thiols was oxidized to disulfides rapidly by this reagent (Table I). Primary alcohol, amine, carboxylic acid, ester, and methoxy functional groups were unaffected during the oxidation of the thiols. The dithiols were oxidizing to the corresponding cyclic disulfides in good yields (Scheme 2 and Table I).

The reactions are relatively clean with no tar formation and no over oxidation to the corresponding disulfide S-oxides, 1,1-dioxides, and sulfonic acids was observed and isolation of products are straightforward.

In conclusion, in this study we have introduced a new and mild reagent for oxidation of thiols to the corresponding disulfide The stability, ease of preparation of reagent, straightforward work-up, mild

TABLE I Oxidation of Thiols **2** with Reagent **1** to Disulfides **3** in Refluxing Acetonitrile[a,b,c]

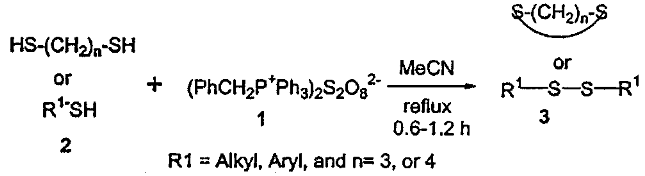
Thiols (2)	Product (3)	Reaction time (h)	Yield[c] (%)	m.p. or b.p./mmHg °C (Lit.)
C_6H_5SH	$C_6H_5SSC_6H_5$	0.5	92	56–60 (59–60)[5]
4-MeC_6H_4SH	4-$MeC_6H_4SSC_6H_4Me$-4	0.8	98	47–48 (46–48)[5]
4-$MeOC_6H_4SH$	4-$MeOC_6H_4SSC_6H_4OMe$-4	0.9	93	44–45 (43.8)[15]
4-$NH_2C_6H_4SH$	4- $NH_2C_6H_4SSC_6H_4$ NH_2-4	1.1	95	75–77 (76–77)[20]
3-MeC_6H_4SH	3-$MeC_6H_4SSC_6H_4Me$-3	0.8	98	−21 (−21)[5]
4-ClC_6H_4SH	4-$ClC_6H_4SSC_6H_4Cl$-4	0.9	98	72–73 (72–73)[18]
2-$MeOOCC_6H_4SH$	2-$MeOOCC_6H_4SSC_6H_4COOMe$-2	0.8	96	198–191 (193)[18]
$C_6H_5CH_2SH$	C_6H_5 CH_2SS $CH_2C_6H_5$	1.1	95	69–70 (69–70)[5]
4-$NO_2C_6H_4SH$	4-$NO_2C_6H_4SSC_6H_4$ NO_2-4	0.75	88	182–184 (182)[5]
2-PyridylSH	2-PyridylSS-Pyridyl-2	0.8	92	52–53 (52–53)[5]
4-PyridylSH	4-PyridylSS-Pyridyl-4	1.1	91	76–77 (76–77)[20]
CyclopentylSH	CyclopentylSSCyclopentyl	1.0	93	105–106 (107–108)
CyclohexylSH	CyclohexylSSCyclohexyl	1.2	87	124 129 (125–130)[15]
HO-CH_2CH_2SH	HO-$CH_2CH_2SSCH_2CH_2OH$	1.2	80	156–148/2(158–163/3.5)[17]
$HOOCCH_2CH_2SH$	$HOOCCH_2CH_2SSCH_2CH_2COOH$	1.0	86	157–159 (1157–159)[17]
$HOOCCH_2SH$	$HOOCCH_2SSCH_2COOH$	1.1	91	138–139 (140)[18]
$CH_3(CH_2)_3SH$	$CH_3(CH_2)_3SS(CH_2)_3CH_3$	1.2	92	94–96/6 (86/3.5)[16]
$CH_3(CH_2)_4SH$	$CH_3(CH_2)_4SS(CH_2)_4CH_3$	1.1	87	117–119/6 (90–92/1)[16]
$CH_3(CH_2)_6SH$	$CH_3(CH_2)_6SS(CH_2)_6CH_3$	1.2	90	152–154/6 (143–147/5)[16]
$CH_3(CH_2)_7SH$	$CH_3(CH_2)_7SS(CH_2)_7CH_3$	1.0	96	152–154/6 (143–147/5)[16]
1-$HSCH_2C_6H_4CH_2SH$-4	Linear polymer[d]	1.2	98	—
$SH(CH_2)_3SH$	1,5-Cyclopentanedisulfide	2.0	70	45–47/6 (–)[19]
	$+\,(-S\,(CH_2)_3S-)_n$[e]		(30 polymer)	65–70 (71–73)[19]
$SH(CH_2)_4SH$	1,6-Cyclohexanedisulfide	1.2	98	30–32 (32–33)[19]

[a] Confirmed by comparison with authentic samples (IR, TLC, and NMR).

[b] Oxidant/thiol (1.0:1.0).

[c] Yield of isolated pure product after chromatography or distillation.

[d] $HSCH_2C_6H_4CH_2S(-SCH_2C_6H_4CH_2S-)_nSCH_2C_6CH_2SH$, [e] $HS(CH_2)_3(-SCH_2CH_2CH_2S-)_n(CH_2)_3SH$.



SCHEME 2

reaction conditions, high yields of the products, and reaction under non-aqueous conditions make this method a useful one for oxidation of thiols and dithiols to disulfides.

EXPERIMENTAL

General

All yields refer to isolated products. Products were characterized by comparison with authentic samples (IR and ^{1}H-NMR spectrum, melting and boiling point, TLC).[5,15–20] All ^{1}H-NMR spectra were recorded at 300 MHz in $CDCl_3$ and CCl_4 relative to TMS (0.00 ppm).

Preparation of Benzyltriphenylphosphonium Peroxodisulfate (BTPPD) 1

A solution of benzyltriphenylphosphonium chloride (8.63 g, 22 mmol) in 75 ml of water was prepared, and then $Na_2S_2O_8$ (3 g, 11 mmol) H_2O (50 mL) was added dropwise to the above solution and the mixture stirred for 20 min at room temperature. The resulting white precipitate was removed by filtration and washed with cooled distilled water (2 × 50 mL), and dried in a desiccator under vacuum over calcium chloride to afford a white powder (9.5 g, 96% yield), which decomposed at 180–182°C to a dark-brown material. ^{1}H-NMR (CD_3CN) δ 6.80-790 (m, 20 H), 4.7 (d, J = 25.6 Hz, 2 H, $C\underline{H}_2$-P), ^{13}C δ 134.5, 133.5, 130.2, 129.6, 129.4, 128.1, 127.7, 127.2, 117.3 (d, J = 85.7 Hz, 2 H, P-$\underline{C}H_2$). Anal calcd for $C_{50}H_{44}O_8P_2S_2$: C, 66.70; H, 4.90; S, 7.35%. Found: C, 66.80; H, 4.90; S, 7.13%.

General Procedure

Oxidation of Thiols with BTPPD 1

The thiol (1 mmol) was added to a stirred solution of BTPPD (0.90 g, 1 mmol) in acetonitrile (5 mL). The reaction mixture was heated at reflux until TLC (eluent: cyclohexane/EtOAc: 8:2) showed complete disappearance of starting material. The reaction mixture was then cooled to room temperature and the mixture solid separated through a short pad of silica gel and washed with acetonitrile (15 mL). The filtrate was evaporated and the resulting crude material was dissolved in CH_2Cl_2 and washed with 5% NaOH solution. The organic layer was dried ($MgSO_4$) and then evaporated to dryness. The crude product was purified by column chromatography on silica gel using a mixture of ethyl acetate and hexane as eluent (10:90) to give disulfides in 70–98% yields (Table I).

REFERENCES

[1] a) J. R. Johnson, W. F. Bruce, and J. D. Dutcher, *J. Am. Chem. Soc.*, **65,** 2005 (1943); P. C. Jocelyn, *Biochemistry of the Thiol Group* (Academic Press, New York, **197).**

[2] a) S. J. Behroozi, W. Kim, and K. S. Gates, *J. Org. Chem.*, **60,** 3964 (1995); b) S. J. Behroozi, W. Kim, J. Dannaldson, and K. S. Gates, *Biochemistry*, **35,** 1768 (1996).

[3] A. R. Hajipour and S. E. Mallakpour, *J. Chem. Research (S)*, **32** (2000).

[4] A. R. Hajipour, I. M. Baltork, and G. Kianfar, *Indian J. Chem.*, **37B,** 607 (1999).

[5] I. M. Baltork, A. R. Hajipour, and H. Mohammadi, *Bull. Chem. Soc. Jpn.*, **71,** 1649 (1998).

[6] S. V. Ley, C. A. Meerholz, and D. H. Barton, *Tetrahedron, Suppl.*, 213 (1981).

[7] A. R. Hajipour and I. M. Baltork, *Phosphorus, Sulfur, and Silicon,* **164,** 145 (2000).

[8] A. R. Hajipour and S. E. Mallakpour, *Mol. Cryst. Liq. Cryst.*, **356,** 371 (2001).

[9] E. Block and J. O'Connor, *J. Am. Chem. Soc.*, **96,** 1135 (1974).

[10] E. Block, *Angew, Chem. Int. Edu. Engl.*, **31,** 1135 (1992).

[11] L. Teuber, *Sulfur Rep.*, **31,** 257 (1992).

[12] a) Y. Kanda and T. Fukuyama, *J. Am. Chem. Soc.*, **115,** 8451 (1993); b) G. Pattenden and A. J. Shuker, *J. Chem. Soc. Perkin Trans. 1*, 1215 (1992).

[13] a) A. R. Hajipour and N. Mahboubkhah, *J. Chem. Research (S)*, 122 (1998); b) A. R. Hajipour, S. E. Mallakpour, and H. Adibi, *Chemistry Lett.*, 460 (2000); c) A. R. Hajipour, S. E. Mallakpour, and S. Khoee, *Chemistry Lett.*, 120 (2000); d) A. R. Hajipour, S. E. Mallakpour, and S. Khoee, *Synlett*, 740 (2000).

[14] a) A. R. Hajipour and N. Mahboobkhah, *Synth. Common.*, **28,** 3143 (1998); b) A. R. Hajipour, I. M Baltork, and G. Kianfar, *Bull. Chem. Soc. Jpn.*, **71,** 2655 (1998); c) A. R. Hajipour and N. Mahboobkhah, *Org. Prep. Proced. Int.*, **31,** 112 (1999); d) A. R. Hajipour, I. M Baltork, and K. Niknam, *Org. Prep. Proced. Int.*, **31,** 335 (1999); e) I. M. Baltork, A. R. Hajipour, and R. Haddadi, *J. Chem. Research (S)*, 102 (1999).

[15] N. Iranpoor and B. Zeynnizadeh, *Synthesis,* 49 (1999).

[16] T. V. Rao, B. Sain, P. S. Murthy, T. S. R. P. Rao, A. K. Jain, and G. C. Joshi, *J. Chem. Research (S)*, 300 (1997).

[17] J. F. Arterburn, M. C. Perry, S. L. Nelson, B. R. Dible, and M. S. Holguin, *J. Am. Chem. Soc.*, **119,** 9309 (1997).

[18] P. Salehi, A. Farrokhi, and Mgholizadeh, *Synth. Commun.*, **31,** 2777 (2001).

[19] N. A. Noureldin, M. Calwell, J. Hendry, and D. G. Lee, *Synthesis*, 1587 (1998).

[20] *Dictionary of Organic Compounds, 5th ed.* (1982). New York: Chapman and Hall.