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Conversion of sulfides to sulfoxides and thiols to disulfides with *o*-xylylenebis(triphenylphosphonium tribromide)

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o-Xylylenebis(triphenylphosphonium tribromide) (**1**) is an efficient reagent for the conversion of thiols to disulfides and sulfides to sulfoxides under neutral and anhydrous conditions in good to excellent yields. Selective oxidation of thiols in the presence of sulfides at room temperature is also observed with this reagent.

Keywords: *o*-xylylenebis(triphenylphosphonium tribromide), oxidation, thiols, sulfides, disulfides, sulfoxides

Most methods for preparing disulfides involve oxidation of thiols. Oxidation of thiols to disulfides without over oxidation is an important process in organic chemistry and biochemistry. Disulfide bond formation is important in peptides[1] and bioactive molecules.[2] This conversion has been accomplished using reagents such as molecular oxygen,[3a] metal ions,[3b] $Bu_3SnOMe/FeCl_3$,[3c] nitric oxide,[3d] halogens,[3e-h] sodium perborate,[3i] borohydride exchange resin (BER)–transition metal salt system,[3j] a morpholine iodine complex,[3k] PCC,[3l] ammonium persulfate,[3m] $KMnO_4/CuSO_4$,[3n] H_2O_2,[3o] solvent-free permangenate,[3p] PVP-N_2O_5,[3q] caesium fluoride–celite, O_2 system[3r] and 2,6-dicarboxypyridinum chorochromate,[3s] *etc.*

Sulfoxides are useful in organic synthesis as an activating group. The oxidation of sulfides to sulfoxides has been extensively investigated. The biggest difficulty associated with the oxidation of sulfides to sulfoxides is the susceptibility of sulfoxide to undergo further oxidation in the reaction mixture to produce a sulfone.[4]

A number of procedures for this transformation from sulfides include treatment with halogens,[5a] *t*-butylhypochlorite,[5b] N-halosuccinimides,[5c] hydrogen peroxide,[5d] *m*-chloroperbenzoic acid,[5e] sodium metaperiodate,[5f] nitrogen tetroxide,[5g] manganese oxide/trimethyl chlorosilane,[5h] tetrabutylammonium peroxydisulfate,[5i] CAN,[5j] $NaClO_2$/ Mn(III) catalyst/ alumina[5k] and magnesium monoperoxy phethalate (MMPP),[5l] *etc.* However some of these methods have disadvantages such as requiring strong oxidizing agents, strongly acidic or basic media, over oxidation, use of expensive reagents, long reaction times, and low yields of products. Therefore the introduction of a clean, mild, and efficient method to synthesise aliphatic, aromatic and heteroaromatic sulfoxides is still in demand. On the other hand, tribromide reagents are prefered in many organic transfer reaction because they are usually crystaline materials which do not have hazards that are associated with liquid bromine. Other advantages of organic phosphonium and ammonium tribromides are that they are easy to handle and maintain the desired stoichiometry.[6] Several tribromides have been synthesised *i.e.* tetramethylammonium tribromide,[7a] tetrabuthylammonium tribromide,[7b] 1,8-diazoabicyclo[5,4,0] undecenehydro-bromide perbromide,[7c] benzyltrimethylammonium tribromide[7d] and 2-carboxyethyltriph-enylphosphonium perbromide.[7e] We now report *o*-xylylenebis(triphenylphosphonium tribromide) as selective and mild reagent for oxidation of sulfides and thiols under neutral and mild conditions.

Results and discussion

o-Xylylenebis(triphenylphosphonium tribromide) (**1**) has been prepared readily from a bromine solution in acetic acid with *o*-xylylenebis(triphenylphosphonium bromide)[8] in a quantitative yield at room temperature. This compound is an orange and stable solid material, which could be stored for months without losing its activity. It is not hygroscopic and no special care is needed for its storage in a closed vessel. This reagent showed an intense UV absorption at 273 nm typical of the tribromide (Br_3^-) group[9] and its presence was confirmed by micro analysis (Scheme 1).

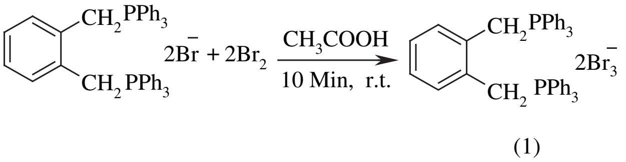
Thiols were oxidised in THF with tribromide (**1**) to give the corresponding disulfides under mild conditions at room temperature (Scheme 2).

The results presented in Table 1 indicate that the present method is equally applicable for the oxidative coupling of aryl thiols (entries **1–3**), alkyl thiols (entries **4–7**) and heterocyclic thiol (entry 8).

Sulfides are also oxidised with this reagent to the corresponding sulfoxides in 80–96% yield in H_2O/THF (Scheme 3, Table 2).

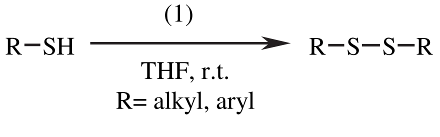
As shown in Table 2, this reaction system can be applied to the oxidation of many types of sulfides such as alkyl aryl sulfides (entries 1–7), dialkyl sulfides (entries 8–11) and heterocyclic sulfide (entry 13). Even an aryl sulfide with an electron withdrawing group such as the nitrile group (entry 7) reacted smoothly to give the corresponding sulfoxide in 80% yield.

Although thiols underwent oxidation at room temperature in less than 6 min, the oxidation of sulfides was slow



(1)

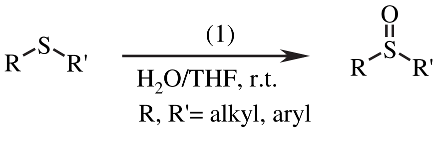
Scheme 1



$$R{-}SH \xrightarrow[\text{THF, r.t.}]{(1)} R{-}S{-}S{-}R$$

R= alkyl, aryl

Scheme 2



Scheme 3

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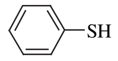
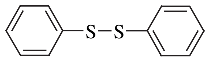
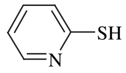
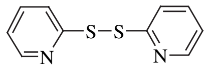
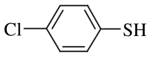
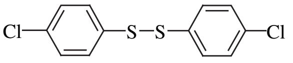
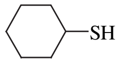
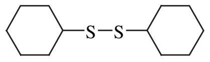
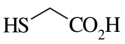
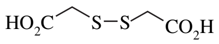
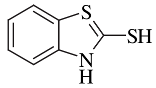
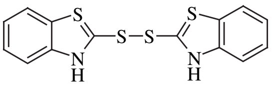
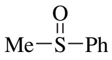
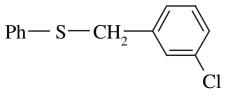
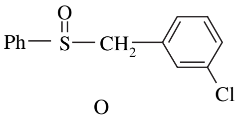
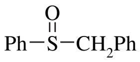
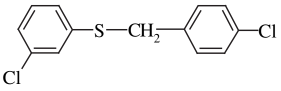
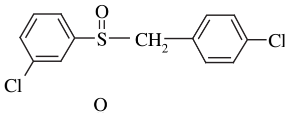
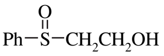
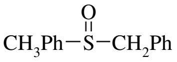
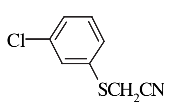
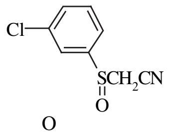
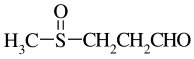
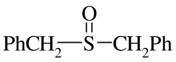
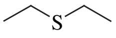
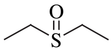
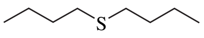
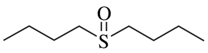
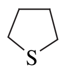
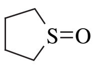
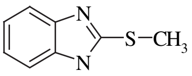
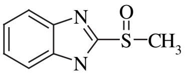
Table 1 Coupling of thiols using *o*-xylylenebis(triphenylphosphonium tribromide)(**1**)

Entry	Substrate	Product	Time/min	Yield/%
1			2	98
2			2	97
3			3	95
4			4	96
5	$C_8H_{17}{-}SH$	$C_8H_{17}{-}S{-}S{-}C_8H_{17}$	2	96
6	$C_4H_9{-}SH$	$C_4H_9{-}S{-}S{-}C_4H_9$	3	97
7			4	95
8			3	96

Yields refer to isolated products; all products were identified by comparing IR, NMR and TLC with those of authentic samples.

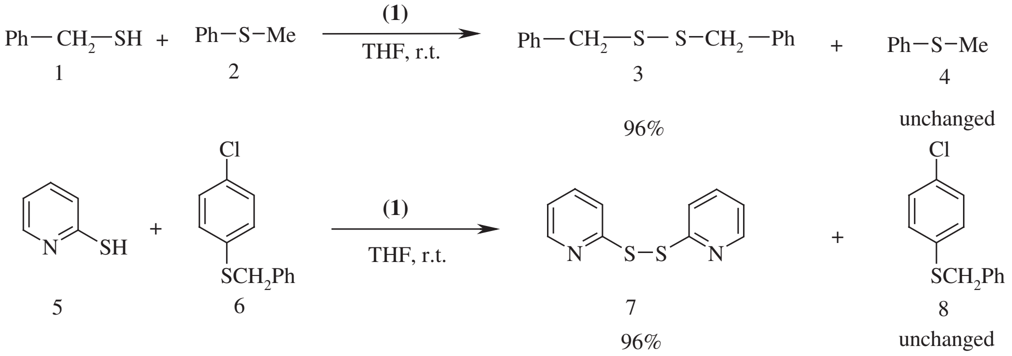
Table 2 Oxidation of sulfides to sulfoxides using *o*-xylylenebis(triphenylphosphonium tribromide) (**1**)

Entry	Substrate	Product	Time/min)	Yield/%
1	$Me{-}S{-}Ph$	 $Me{-}\overset{O}{\overset{\|}{S}}{-}Ph$	5	98
2			15	90
3	$Ph{-}S{-}CH_2Ph$	 $Ph{-}\overset{O}{\overset{\|}{S}}{-}CH_2Ph$	10	96
4			15	90
5	$Ph{-}S{-}CH_2CH_2OH$	 $Ph{-}\overset{O}{\overset{\|}{S}}{-}CH_2CH_2OH$	5	92
6	$CH_3Ph{-}S{-}CH_2Ph$	 $CH_3Ph{-}\overset{O}{\overset{\|}{S}}{-}CH_2Ph$	5	95
7			40	80
8	$H_3C{-}S{-}CH_2CH_2CHO$	 $H_3C{-}\overset{O}{\overset{\|}{S}}{-}CH_2CH_2CHO$	6	95
9	$PhCH_2{-}S{-}CH_2Ph$	 $PhCH_2{-}\overset{O}{\overset{\|}{S}}{-}CH_2Ph$	8	96
10			10	96
11			10	96
12			5	95
13			10	93

Yields refer to isolated products; all products were identified by comparing IR, NMR and TLC with those of authentic samples.

and required a higher number of equivalents of oxidant. This reagent selectively oxidised thiols in the presence of sulfides at room temperature. When a mixture of equimolar amounts of thiols entries 1 or 5 of Table 1 in the presence of sulfides entries 2 or 6 of Table 2 were treated with (**1**) only the thiols were selectively oxidised to the corresponding disulfides and the sulfides remained unchanged (Scheme 4).

In order to show the advantages and drawbacks of this reagent over some other oxidants, we have compared some of our results with those reported in the literature (Table 3).



Scheme 4

Table 3 Comparison of tribromide (1) with some of other reagents for oxidation of thiols and sulfides

Substrate	Conditions	Time min/Yield%	Reagent	Ref.
PhSH	THF/r.t.	2/98	(1)[a]	–
PhSH	CH_3CN/r.t.	120/99	$Bu_3SnOMe/FeCl_3$	3c
PhSH	CH_2Cl_2/r.t.	114/97	PCC[b]	3l
PhSH	Solid state	10/95	$(NH4)_2S_2O_8$	3m
PhSH	CH_3CN/20 ˚C	270/93	Caro,s acid/SiO_2	10a
Cyclohexane thiol	THF/r.t.	4/96	(1)	–
Cyclohexane thiol	Solid state	20/94	*QFC*/SiO_2[c]	10b
Cyclohexane thiol	CH_3CN	120/92	Sodium perborate	10c
Cyclohexane thiol	CH_3CN/rt	18/91	2,6-DCPCC[d]	3s
PhsMe	THF/H_2O/r.t.	5/96	(1)	–
PhsMe	CH_3OH/20 ˚C	60/99	MnO_2-TMCS[e]	5h
PhsMe	CH_2Cl_2/r.t.	90/98	(n-Bu4N)$_2S_2O_8$	5i
PhsMe	CH_2Cl_2/r.t.	60/100	CAN[f]	5j
PhsMe	CH_2Cl_2	15/89	$NaClO_2$/Allumina	5k
PhsMe	CH_2Cl_2/H_2O/ r.t	20/93	HMTAB[g]	11c

[a] *o*-Xylylenebis(triphenylphosphonium tribromid); [b] Pyridinium chlorochromate; [c] Quinolinium fluorochromate; [d] 2,6-Dicarboxypyridinium chlorochromate; [e] Trimethylchlorosilane; [f] Ceric ammonium nitrate; [g] Hexamethylenetetramine-bromine;

As shown in this Table, *o*-xylylenebis(triphenylphosphonium tribromide) in comparison with other similar reagents, oxidised both thiols and sulfides in shorter reaction time and under milder reaction conditions.

In conclusion, we have shown that this compound is an efficient, easily prepared and inexpensive reagent for the oxidation of aliphatic, aromatic and heteroaromatic thiols and sulfides to the corresponding disulfides and sulfoxides at room temperature. It can oxidise thiols almost quantitativly irrespective of the presence of sulfides. Besides, the rate of oxidation reactions are enhanced using this reagent in comparison with other similar compunds.[11]

Experimental

All yields refer to isolated products after purification. Products were characterised by comparison with authentic samples (IR and ^{1}H NMR spectra, TLC, melting and boiling points). All ^{1}H NMR were recorded at 90 MHz in CCl_4 relative to TMS and IR spectra were recorded on a Shimadzu 435 IR spectrophotometer.

General procedure for the preparation of o-xylylenebis(triphenylphosphonium tribromide)

A solution of o-xylylenebis(triphenylphosphonium bromide) (24.2 mmol, 19 g) in 100 ml of acetic acid was prepared and bromine (96.8 mmol, 8.04 ml) in acetic acid (100 ml) was added dropwise to the above solution which was then stirred for 15 minutes at room temperature. The resulting precipitate was filtered, washed with water (3 × 30 ml) and dried in a desiccator under vacuum over calcium chloride to afford an orange powder (33.12 g 98.9%), which decomposed at 110–112 °C to a dark-brown material. The content of active oxidising agent (Br_3^-) was determined by a titrimetric method.[12] Anal Calcd for $C_{44}H_{38}P_2Br_6$ C: 46.7 H: 3.4 found C: 47.7 H: 3.5

General procedure for the oxidation of thiols and sulfides with o-xylylenebis(triphenyl- phosphonium tribromide) (**1**)

In a round-bottomed flask, a solution of thiols (1 mmol) in THF (10 ml) or sulfides (0.5 mmol) in THF/H_2O (10 ml) was treated with o-xylylenebis(triphenylphosphonium tribromide) (1) (0.5 mmol) and the mixture stirred at room temperature for the time specified in the Tables 1 and 2. The progress of the reaction was monitored by GC or TLC. The colour of the solution gradually faded and then completely decolourised during the reaction. After the reaction was completed, the mixture was filtered. To the filtrate was added 5% aqueous $Na_2S_2O_3$ solution (5 ml), the organic layer was separated, the remaining aqueous layer was extracted twice with diethyl ether (2 × 20 ml) and the washings were added to the organic layer. The combined organic layer was dried on magnesium sulfate, and evaporated under vacuum to give the corresponding disulfide in almost pure form. If nececssary, the product was purified by column chromatography.

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