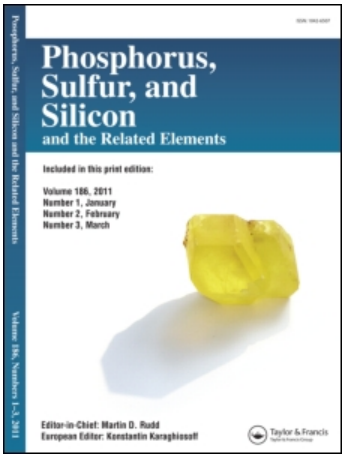

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Carboxy Pyridinium Bromide Perbromide Reagents, Part I: Selective Oxidation of Thiols and Sulfides

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Efficient and convenient oxidation of aliphatic and aromatic thiols to disulfides and of sulfides to sulfoxides with pyridinium hydrobromide perbromide (PHBP), nicotinic acid hydrobromide perbromide (NAHBP), and 2,6-dicarboxy pyridinium hydrobromide perbromide (DCPHBP) in a solvent or under solvent free conditions and at ambient temperature is introduced.

Keywords Bromide perbromide; disulfide; thiols; oxidative coupling; solvent-free condition; sulfoxides

INTRODUCTION

Disulfides are useful reagents in organic synthesis[1,2] and essential moieties of biologically active compounds for peptide and protein stabilization.[3] As disulfides are relatively more stable to organic reactions such as oxidation, alkylation and acylation compared to the corresponding free thiols, the thiol group can conveniently be protected as a disulfide.

So far, various reagents for the oxidative coupling of thiols to disulfides have been described, e.g. iodine/hydrogen iodide,[4] neat bromine,[5a] bromine/aqueous potassium hydrogen carbonate,[5b] bromine/SiO_2,[5c] $FeCl_3$/NaCl,[6] $KMnO_4/CuSO_4$,[7] hydrogen peroxide in tetrafluoroethanol,[8] Caro's acid/SiO_2,[9] TMSCl and cyanuric chloride,[10] HMDS/DMSO,[11] $Cu(NO_3)_2 \cdot N_2O_2$,[12] I_2/morpholine,[13] piperazinium dichromate,[14] DMSO,[15] and 2,6-dicarboxypyridinium chlorochromate.[16] However, most of these reagents suffer from disadvantages such as long reaction times and low yields, toxicity, availability, difficult work-up, difficult preparation and instability.

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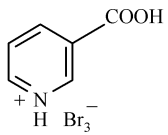
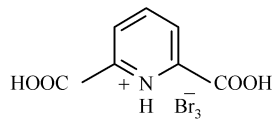
On the other hand, the chemistry of sulfoxides has attracted the attention of organic chemists for a long time. The interest in this chemistry and in the preparation of sulfoxides is due to the fact, that sulfoxides are often part of natural products and drugs, and also have unique reactivity as a functional group for various transformations into organosulfur compounds.[17] The selective preparation of sulfoxides from the corresponding sulfides was performed with a variety of reagents. However, many of these reagents need a careful control of the reaction conditions such as temperature and quantity of the reagent in order to avoid the formation of sulfones as side products.[18] Moreover, the majority of oxidizing reagents are incompatible with other sensitive functionalities (e.g., hydroxy group, aldehyde, phenol ether) present in the molecule of the organic substrate.

So far, a few amine based hydrobromide perbromide reagents have been prepared and used for bromination of alkenes, activated aromatic rings and aldehydes or ketones.[19,20] The nature of the amine not only affects the oxidation property of the perbromide ion but also determines the stability of the reagent, which is inversely related to the donor strength of the associated amine.

Pyridinium hydrobromide perbromide (PHBP) has been introduced for selective bromination and oxidation/dehydration reactions.[19,20] In continuation of our previous investigations on the oxidative coupling of thiols,[9,14] we now present pyridinium hydrobromide perbromide (PHBP), nicotinic acid hydrobromide perbromide (NAHBP), and 2,6-dicarboxypyridinium hydrobromide perbromide (DCPHBP) as mild and stable reagents for the selective oxidation of thiols to disulfides, and of sulfides to sulfoxides in high to excellent yields. Both, nicotinic acid hydrobromide perbromide (NAHBP) and 2,6-dicarboxypyridinium hydrobromide perbromide (DCPHBP), are orange solids, which are stable for several months in glass bottle at room temperature (Scheme 1).



(NAHBP)



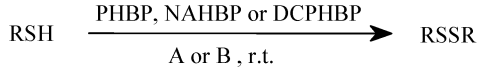
(DCPHBP)

SCHEME 1

RESULTS AND DISCUSSION

This paper describes the preparation and the synthetic potential of PHBP, NAHBP and DCPHBP for the oxidation of aliphatic and aromatic thiols to disulfides under solvent-free conditions, as well as the oxidation of sulfides to sulfoxides in THF/H_2O.

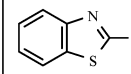
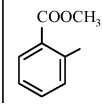
The convenient oxidation of thiols to the corresponding disulfides is achieved using these reagents both in an organic solvent and under solvent free conditions at room temperature (Scheme 2).



A = solvent free condition
B = organic solvent

	R
a	Ph
b	4-$CH_3C_6H_4$
c	4-ClC_6H_4
d	4-BrC_6H_4
e	3-$CH_3C_6H_4$
f	2-naphthyl
g	$PhCH_2$
h	cyclohexyl

	R
i	2-propyl
j	*n*-C_4H_9
k	*n*-C_5H_{11}
l	*n*-C_8H_{17}
m	$HOOCCH_2$
n	$HOOCCH_2CH_2$
o	$HOCH_2CH_2$

	R
p	
q	
r	

SCHEME 2

The solvent-free procedure is very suitable for long chain aliphatic thiols, which are usually insoluble in polar solvents, and therefore difficult to handle when using conventional methods (Table I). The results presented in Table I indicate that this method is equally applicable for the oxidative coupling of alkyl, aryl, and heterocyclic thiols. The reactions were preformed under mild conditions and proceed in high to excellent yields. The reagents selectively oxidized the thiols to the corresponding disulfides without further oxidation or bromination of the aromatic rings.

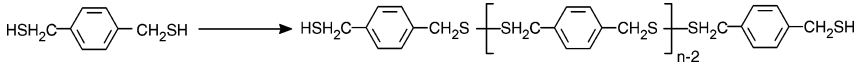
It is worth mentioning that, when 2-mercaptoethanol (Table I, **o**) was treated with these reagents in a solvent or under solvent free conditions only oxidative coupling took place and the corresponding disulfide was obtained as the only product.

TABLE I Oxidative Conversion of Thiols to Disulfides with Hydrobromide Perbromide Reagents[a,b]

	PHBP		NAHBP		DCPHBP	
	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)
a	90	3	94	4	89	3
b	93	5	95	5	93	5
c	93	7	96	5	94	5
d	93	7	93	5	92	4
e	91	3	91	4	89	5
f	93	5	94	6	95	5
g	88	7	89	8	91	7
h	92	10	87	10	94	8
i	79	6	75	8	—	—
j	85	6	82	8	—	—
k	89	8	81	10	83	5
l	90	9	93	10	91	7
m	75	7	71	7	73	9
n	77	8	74	10	—	—
o	—	—	90	5	85	3
p	81	30	83	25	77	18
q	72	30	73	20	75	25
r	85	20	89	15	—	—

[a]Yields refer to isolated products. [b]Reactions were carried out under solvent-free conditions.

Surprisingly, functional groups such as halogen, OH, CO_2Me, and heterocyclic rings are unaffected under the reaction conditions. In the case of *p*-xylylene dithiol the corresponding polymer was obtained due to intermolecular oxidation (Scheme 3).

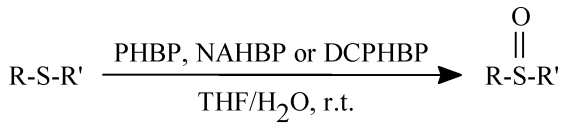


SCHEME 3

Some experiments with thiophenol and *p*-chlorothiophenol were also conducted in water as solvent and afforded the corresponding disulfides in high yields.

Using these bromide perbromide reagents, organic sulfides can be readily oxidized to the corresponding sulfoxides in THF/H_2O at room temperature in high to excellent yields (Scheme 4).

The results are summarized in the Table II. This reaction is applicable to dialkylsulfides, alkylarylsulfides, and diarylsulfides. In addition,



R, R' : See Table II

SCHEME 4

sulfides containing a strong electron-withdrawing group like NO_2 react readily to give the corresponding sulfoxide in high yield.

In order to show the advantages and drawbacks of these reagents compared to some other oxidants, we have compared some of our results with those reported in the literature for the oxidation of thiols (Table III).

The tribromides PHBP, NAHBP, and DCPHBP were prepared from hydrobromic acid (48%), bromine, and the respective pyridine derivative according to the method reported for PHBP.[18] The tribromide content was determined by known iodometric methods. The reagents are isolated as orange-red, stable crystals and can be stored in a glass bottle for several months without any loss of activity.

Investigations about the possible use of these perbromide reagents in further oxidation, bromination and deprotection reactions are underway.

TABLE II Oxidation of Sulfides to Sulfoxides Using PHBP, NAHBP, and DCPHBP[a]

R	R′	PHBP Yield (%)/Time (h)	NAHBP Yield (%)/Time (h)	DCPHBP Yield (%)/ Time (h)
Ph	Me	89(1.5)	91(1)	91(1)
Ph	Bn	90(1.5)	92(1)	89(1.5)
4-$CH_3C_6H_4$	Bn	88(1.5)	94(1)	93(1.5)
Bn	Bn	86(1.5)	89(1.5)	92(1.5)
Ph	-CH_2CH_2OH	94(1)	95(0.5)	94(0.5)
Ph	2,4-$NO_2C_6H_4$	79(2)	82(2)	78(2)
-$CH_2CH_2CH_2CH_2$-		84(1.5)	87(1)	89(1)
n-Bu	*n*-Bu	88(1.5)	82(1)	81(1)
Ph	-CH_2CH_2CN	85(2)	83(1.5)	86(2)

[a]Yields refer to isolated products.

TABLE III Comparison of the Perbromide Reagents with Some Other Reported for the Oxidation of Thiophenol

Reagent	Condition	Time (min)	Yield (%)	Reference
2,6-DCPCC[a]	CH_3CN/r.t.	8	93	16
$Bu_3SnMe/FeCl_3$	CH_3CN/r.t.	120	99	21*a*
PCC[b]	CH_2Cl_2/r.t.	114	97	21*b*
$(NH_4)_2S_2O_8$	Solvent free	10	79	21*c*
Caro's acid/SiO_2	CH_3CN/r.t.	270	93	9
Piperazinium dichromate	$CHCl_3$/reflux	210	92	14
PHBP	Solvent free	3	90	—
NAHBP	Solvent free	4	94	—
DCPHBP	Solvent free	3	89	—

[a]2,6-Dicarboxypyridinium chlorochromate; and [b]pyridinium chlorochromate.

EXPERIMENTAL

All products were identified by comparison of their physical and spectral data with those of authentic samples. IR spectra were determined on a Brucker FTIR-85 spectrometer. ^{1}H NMR spectra were recorded with a BRUKER DRX-500 AVANCE spectrometer at 500 MHz (^{1}H) and with a JEOL FT-NMR instrument at 90 MHz (^{1}H) and at 22.4 MHz (^{13}C).

General Procedure for the Preparation of NAHBP and DCPHBP

To a cooled solution (ice bath) of nicotinic acid or 2,6-dicarboxypyridine (0.1 mol) in acetic acid (30 mL) was added with stirring (48%) HBr (10 mL). Then, a solution of bromine (0.1 mol) in acetic acid (5 mL) was added dropwise and the mixture was stirred for 10 min at room temperature. The resulting orange solid was filtered off, washed with acetic acid (5 mL), and then dried in a desiccator to give a nonhygroscopic powder.

NAHBP

m.p. = 140–142°C, FT-IR (KBr): υ = 3499, 3379, 1720, 1607, 1390, 1240, 1214, 1179, 1120, 925, 746, 669 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.49 (dd, J = 7.9 Hz, J = 4.8 Hz, 1H), 8.24 (dd, J = 7.9, J = 2.0 Hz, 1H), 8.75 (dd, J = 4.7 Hz, J = 1.6 Hz, 1H), 9.06 (dd, J = 2.0 Hz, J = 0.6 Hz, 1H), 13.30 (br, 2H).

DCPHBP

m.p. = 118–122°C, FT-IR (KBr): υ = 2362, 1706, 1389, 1269, 1233, 916, 746, 669 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.16 (t,J = 7.3 Hz, 1H), 8.21 (d, J = 7.3 Hz, 2H), 13.30 (br, 3H).

General Procedure for the Oxidation of Thiols by PHBPB, NAHBP and DCPHBP under Solvent Free Conditions

The hydrobromide perbromide reagent (1 mmol) was added to the thiol (1 mmol) in a mortar. The mixture was kept for the appropriate period of time (Table I) at room temperature. The progress of the reaction was followed by dissolving a sample in ether and using thin layer chromatography on silica gel (petroleum ether). After completion of the reaction, diethyl ether (20 mL) was added and the solid was separated by filtration. The filtrate was washed with water (2 × 15 mL). The organic layer was separated and dried ($MgSO_4$). Finally, evaporation of the solvent gave the disulfides in 71–96% yields in almost pure form. Further purification was achieved by recrystallization from methanol.

General Procedure for the Oxidation of Thiols in Diethyl Ether with PHBP

In a round-bottomed flask, a solution of the thiol (1 mmol) in diethyl ether (10 mL) was treated with the hydrobromide perbromide (1 mmol) and the resulting mixture was stirred at room temperature. The progress of the reaction was monitored by TLC (petroleum ether). On completion, the reaction mixture was filtered and the solid separated was washed with diethyl ether (10 mL). The filtrate was washed with water (2 × 10 mL), dried over $MgSO_4$, and evaporated to give the corresponding disulfide. Further purification was achieved by recrystallization from methanol.

General Procedure for the Oxidation of Sulfides to Sulfoxides

In a round-bottomed flask a solution of the sulfide (1 mmol) in a mixture of THF (10 mL) and H_2O (5 mL) was treated with the perbromide reagent (1 mmol) and the mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. The reaction mixture was filtered and the solid separated was washed with diethyl ether (25 mL). The filtrate was washed with water (2 × 10 mL) and dried over $MgSO_4$. Evaporation of the solvent gave the corresponding sulfoxide in almost pure form.

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