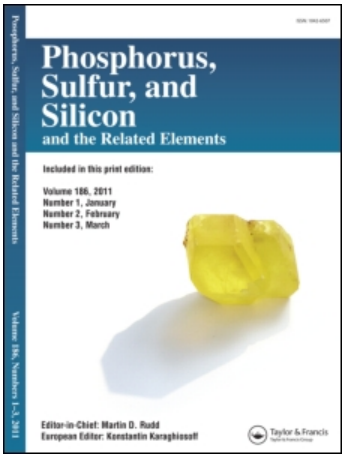

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Mild and Highly Efficient Preparation of Symmetrical Disulfides and Diselenides Using Bipyridinum Hydrobromide Perbromide as a New Oxidative Reagent

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Mild and Highly Efficient Preparation of Symmetrical Disulfides and Diselenides Using Bipyridinum Hydrobromide Perbromide as a New Oxidative Reagent

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A rapid and efficient method for the large-scale synthesis of symmetrical disulfides and diselenides is developed involving oxidative coupling of corresponding thiols and selenols using bipyridinium hydrobromide perbromide (BPHP).

Keywords Diselenide; disulfide; oxidative coupling; selenols; thiols

INTRODUCTION

Oxidative coupling of thiols and selenols to the corresponding disulfides and diselenides is very important in biology,[1–3] organic synthesis,[4–13] and industries.[14–16] Due to ease of preparation, disulfides are usually used as sulfenylating agent for carbonyl compounds.[17–20] There are various methods for the oxidative coupling of thiols, but most of them suffer from one or more disadvantages such as unavailability of reagents, unfavorable conditions for preparation of the reagent, toxicity, high cost, long reaction and/or monitoring period, over-oxidation, and cumbersome work-up procedures. Most reagents are metallic and are toxic for the environment,[21] while, others such as Br_2 are non-metallic[22] and encounter the difficulty in handling and isolation.

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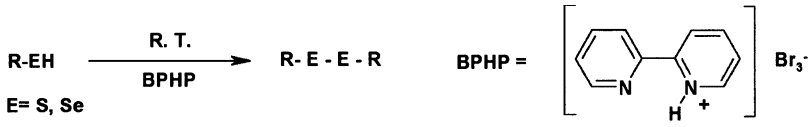
Herein, we introduce a new reagent, bipyridinium hydrobromide perbromide (BPHP), for selective oxidative coupling of thiols and selenols to their corresponding disulfides and diselenides (Scheme 1, Table I). In some cases (Table I, entries 3–4 and 16–17) the activity of the reagent in large-scale synthesis was investigated.



SCHEME 1

The utility of the BPHP in the oxidation of aromatic, aliphatic, benzylic, heterocyclic thiols, and aromatic selenols was tested. The results are shown in Table I. Aromatic thiols, independent of electronic and steric effects of the substituents, react well to afford the corresponding disulfides in high yields (Table I, entries 1–7). It is important to note that no oxidation of an amino group was observed (Table I, entry 4). Therefore, the high selectivity, in addition to the ease of oxidation compared to the previously reported reagents,[23] is a remarkable advantage of this reagent.

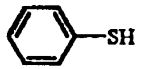
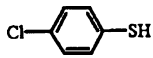
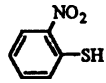
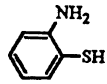
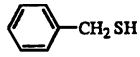
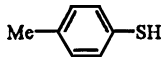
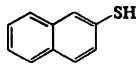
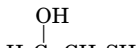
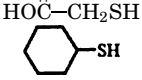
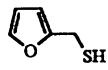
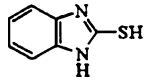
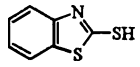
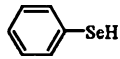
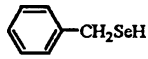
In the case of aliphatic thiols, it seems that the reaction depends on the electronic properties of the thiols.[24] Comparison of the results obtained with entries 9–11 reveals that the reactivity decreased with increasing the electron withdrawing property of the substituents which follows the order Pr > $CH_2OH \gg$ COOH.

One of the most important advantages of our study comes from the oxidative coupling of the two benzimidazoles, 2-mercaptobenzimidazole and 2-mercaptothiobenzimidazole (entries 14 and 15, respectively). They were oxidized to their corresponding disulfides in acetonitrile for only 5 minutes at room temperature by BPHP. The disulfides were isolated in high yields (85 and 90%, respectively).

In order to investigate the potential of BPHP in large-scale synthesis of disulfides and diselenides, the reactions were carried out using about 50 mmol of each entry 3, 4, 16, and 17. The yields were high to excellent (80, 83, 85, and 85%, respectively). So, it is concluded that BPHP is very effective for large-scale synthesis of these compounds.

It also should be emphasized that the reactions could be performed cleanly and controlled to stop at the disulfide and diselenide stage. Overoxidation has not been observed, even when the reactions were carried out in different conditions (entries 1 and 8).

TABLE I Oxidative Coupling of Thiols and Selenols by BPHP[a]

Entry	RE-H	Time (min)	RE-ER yield (%)[b]	M.P. (°C)	Lit. M.P. (°C)
1[c]		10	88	61	60–61[10,22]
2		10	85	72	70–71[28]
3		15	90	198	—
4		15	95	92	91–92[28]
5		20	88	70	71–71[28]
6		5	95	45	43–44[8]
7		5	95	144	143–144[29]
8	$nC_8H_{17}SH$	30	75	Oil	Oil[33]
9[d]	nC_4H_9S	15	92	Oil	Oil[21,22]
10		35	70	Oil	Oil[22]
11		40	65	106	107[36]
12		15	90	126	124–129[30]
13		30	70	Oil	Oil[9]
14		5	85	201	200[31]
15		5	90	180	180–182[32]
16		5	95	56	56[26]
17		5	95	92	91–93[34]

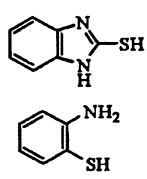
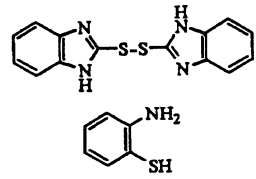
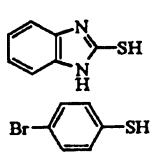
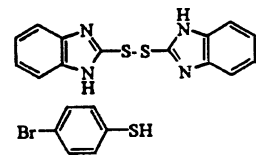
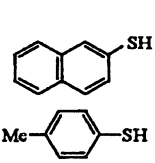
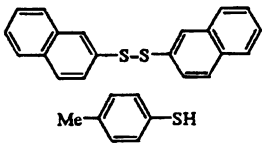
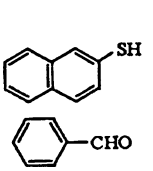
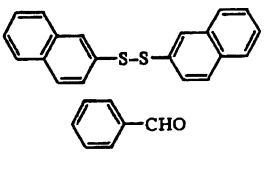
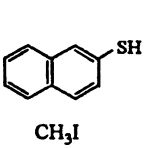
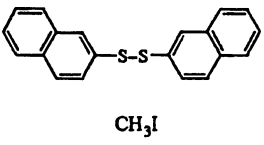
[a]All reactions were carried out at room temperature using oxidant to substrate molar ratio 1:2 in acetonitrile except indicated. All products were identified by their IR and NMR spectral data and comparison of their mp with published data.

[b]Isolated yields.

[c]Reaction was performed under solvent-free condition.

[d]CH_2Cl_2 was used as solvent.

TABLE II Competitive Oxidative Coupling of Thiols with BPHP[a]

Entry	Substrates (1:1)	Products	Time (min)	Yield (%)[b]
1			10	89 100
2			10	90 100
3			20	80 100
4			10	92 100
5			5	100 100

[a]Oxidant to substrate molar ratio is 1:2.
[b]Isolated yield.

In order to evaluate the intermolecular chemoselectivity of the reagent, the competitive reactions were carried out and the results are summarized in Table II. It is interesting to note that cross-coupling reaction was not achieved under the reaction conditions (Table II, entries 1–3). Furthermore, in this competitive reaction, sensitive groups to oxidation, like anilines or aldehydes, are stable and remained intact in the reaction mixture (Table II, entries 1, 4). Such selectivity has not been reported previously and could be considered a useful practical achievement in disulfide synthesis.

Recently a convenient procedure for the synthesis of organic sulfide from alkyl halides and aryl disufides has been reported.[35] The authors have suggested a S_N2 type mechanism is responsible for these reactions. We encouraged to examine the possibility of one pot conversion of thiols to the coressponding sulfide using methyliodide as a strong nucleophile suitable for such mechanism (Table II, entry 5). The result shows that the nucleophile remained intact and the reaction performed and controlled to stop at the disulfide stage.

EXPERIMENTAL

Melting points were recorded on Electrothermal apparatus and were uncorrected. All chemicals are commercially available and used without further purification. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 200 MHz NMR Spectrometer. Elemental analyses were performed using CHN Herause rapid model. Thin layer chromatography was performed on precoated silica gel Fluorescent 254 nm (0.2 mm) on aluminum plates. All yields referred to isolated pure products.

Preparation of Bipyridinium Hydrobromide Perbromide (BPHP)

To a flask containing bipyridine (7.8 g, 50 mmol) cooled in an ice-salt bath hydrobromic acid (5.0 ml, 107 mmol) was added slowly. The reaction was stirred for about 5 min, and then bromine (5.5 ml, 107 mmol) was added dropwise. The temperature was maintained at about $-5^\circ C$. A bulky orange solid was formed immediately which was dried *in vacuo.* Mp 140–143°C (decomp). Yield 16.7 g (72%). Anal calc. For $C_{10}H_9N_2Br_3$: C, 30.26%; H, 2.29%; N, 7.06%. Found: C, 30.47%; H, 2.35%; N, 7.03% (mean value of two analyses).

Reaction of 4-Chlorothiophenol with BPHP—A Typical Procedure

To a stirred solution of 4-chlorothiophenol (0.29 g, 2 mmol) in acetonitrile (5 ml) BPHP (0.60 g, 1.5 mmol) was added, and the mixture was stirred at room temperature for 10 min. A yellowish solid was formed and was treated with a 1:1 mixture of ether and water (2 ml). The reaction mixture was extracted with ether (3 × 10 ml). The organic layers were combined together and dried over anhydrous $MgSO_4$. The solvent was removed by a rotary evaporator to afford the corresponding disulfide in 85% (0.22 g) yield, mp 72°C (Lit.[25] mp 74°C).

Reaction of Selenophenol with BPHP—A Typical Procedure for Large-Scale Synthesis

To a stirred solution of selenophenol (5.0 ml, 47.2 mmol) in acetonitrile (30 ml) BPHP (14.0 g, 35.4 mmol) was added, and the mixture was stirred at room temperature for 10 min. The solid was treated with a 1:1 mixture of ether and water (40 ml). The reaction mixture was extracted with ether (5 × 20 ml). The organic layers were combined and dried over anhydrous $MgSO_4$. The solvent was removed by a rotary evaporator to afford a white solid in 85% (6.25 g) yield, mp 64–65°C (Lit.[26] m.p. 65°C).

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