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Base-free oxidation of thiols to disulfides using selenium ionic liquid

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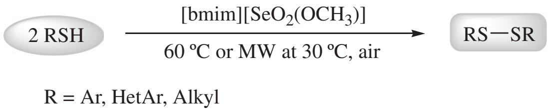
ABSTRACT

We present here the results on the use of 1-*n*-butyl-3-methylimidazolium methylselenite, [bmim][$SeO_2(OCH_3)$], in the synthesis of symmetrical disulfides starting from thiols. This efficient and improved method is general for aromatic, aliphatic, and functionalized thiols affording the disulfides in good to excellent yields after easy work up. The use of a microwave accelerates the reaction and the [bmim][$SeO_2(OCH_3)$] was reused for further oxidation reactions.

Thiols and disulfides are important in both biological[1] and chemical processes.[2] Disulfides are useful reagents in organic synthesis[2] and essential moieties of biologically active compounds for peptide and protein stabilization.[1] As disulfides are relatively more stable toward organic reactions, such as oxidation, alkylation, and acylation, compared to the corresponding free thiols, the thiol group can conveniently be protected as a disulfide. Besides, there are a large number of commercially available thiols and the interconversion between thiols and disulfides is easy.[3] These aspects are responsible for the continuous interest in the development of new, selective, and efficient protocols for the preparation of disulfides.[2,4,5]Recently reported procedures to obtain symmetrical disulfides involve the use of anhydrous potassium phosphate,[4a] potassium permanganate,[4b] molecular bromine supported on silica gel,[4c] *N*-phenyltriazolinedione,[4d] VO(acac)$_2$,[4e] trichloroisocyanuric acid,[4f] nitric acid,[4g] 1,3-dibromo-5,5-dimethylhydantoin,[4h] basic alumina,[4i] CsF–Celite,[4j] and montmorillonite K10.[4k] Additionally, cleaner protocols under solvent-free conditions were described.[4d,6] These methods use *N*-phenyltriazolinedione,[4d] pyridinium chlorochromate,[6a] 1,3-dibromo-5,5-dimethylhydantoin,[6b] SO_2Cl_2,[6c] trichloronitromethane,[6d] $KMnO_4/MnO_2$,[6e] $KMnO_4$ supported on montmorillonite K10,[6f] catalytic amount of iodine, and $CeCl_3{\cdot}7H_2O$ in graphite,[6g] and KF/Al_2O_3[6h] as catalysts. Thus, there is still an attention in developing green methods that would produce the desirable disulfides in high yields.

In this way, ionic liquids (ILs) constitute an interesting alternative for this reaction. Because product isolation or catalyst recycling is very easy in ILs and, in some cases, rate accelerations and/or selectivity improvements are also observed, they are regarded as environmentally friendly green solvents.[7] In this context, the use of [bmim][BF_4] as a solvent for the oxidation of thiols in the presence of a base was described.[8] Recently, we have reported the use of the new cationic selenium-based acidic ionic liquid phenyl butyl ethyl selenonium tetrafluoroborate, [pbeSe][BF_4], as an efficient catalyst in several acid-catalyzed reactions.[9] Besides, the application of the ionic liquid containing anionic selenium-based [bmim][$SeO_2(OCH_3)$] in the oxidative carbonylation of aniline was also described.[10] The selenium-containing ionic-liquids shown superior catalytic performance and were reused without losing their initial activity.[10] Due to our interest in new applications for selenium-based ionic liquids,[9] we decide to study the use of [bmim][$SeO_2(OCH_3)$][10] as the solvent in the oxidation of thiols to symmetrical disulfides (Scheme 1).



Scheme 1. General scheme of reaction.

Initially, we chose benzenethiol as a substrate to establish the best condition for the air oxidation reaction in the presence of 1.0 mL of [bmim][$SeO_2(OCH_3)$]. Thus, a mixture of benzenethiol (1.0 mmol) and [bmim][$SeO_2(OCH_3)$] was stirred for 12 h at room temperature furnishing diphenyl disulfide **1a** in 45% yield. This unexpected, new result showing the ionic liquid acting both, as a solvent and catalyst, encouraged us to investigative the effect of the temperature in this base-free oxidation. To our satisfaction,

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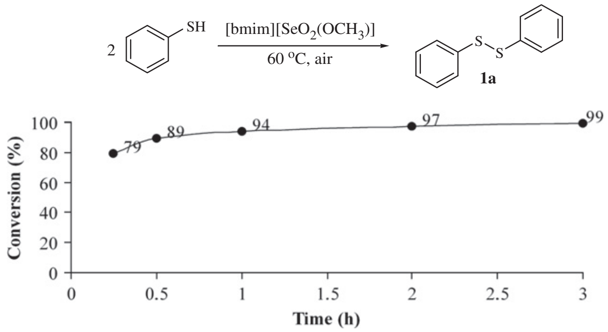
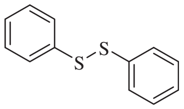
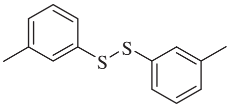
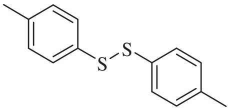
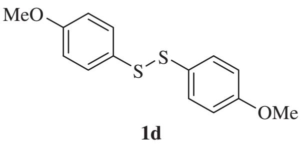
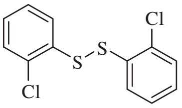
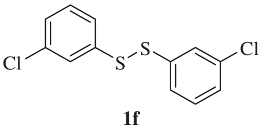
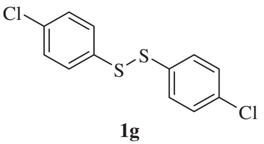
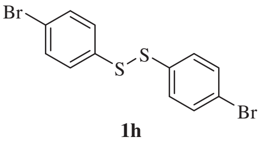
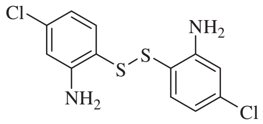
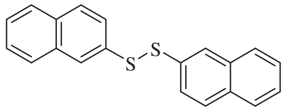
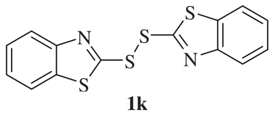
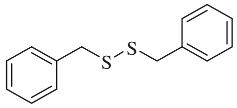
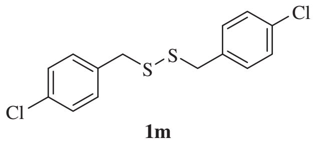
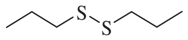
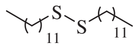
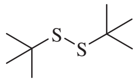
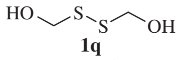
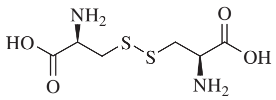


Figure 1. Plot of conversion versus time for the oxidation of benzenethiol (determined by GC).

Table 1
Synthesis of disulfides **1a–r** using [bmim]SeO$_2$(OCH$_3$)] according method A[a]

Entry	Time (h)	Product yield [lit.]
1	3	 **1a** 98%[12]
2	2	 **1b** 99%[13]
3	4	 **1c** 99%[14]
4	3	 **1d** 99%[15]
5	4	 **1e** 98%[14]
6	4	 **1f** 93%[16]
7[b]	3	 **1g** 99%[17]
8[b]	3	 **1h** 99%[18]
9	14	 **1i** 78%[19]
10	5	 **1j** 88%[20]
11[b]	2	 **1k** 99%[21]
12	4	 **1l** 98%[14]
13	4	 **1m** 87%[22]
14	3	 **1n** 99%[23]
15	4	 **1o** 84%[24]
16	4	 **1p** 80%[18]
17	18	 **1q** 85%[25]
18	8	 **1r** 87%[20]

[a] Yields are given for pure isolated products.

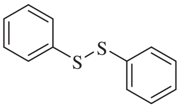
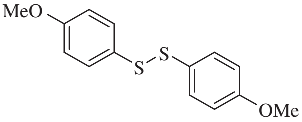
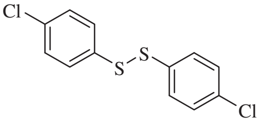
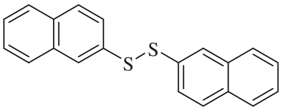
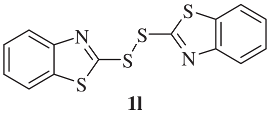
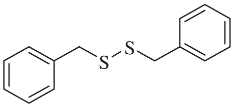
[b] Reaction was performed at 100 °C.

at a gentle heating (60 °C), the reaction proceeded slowly furnishing the desired diphenyl disulfide **1a** in 98% isolated yield after 12 h. In order to obtain an efficient protocol in terms of energy economy, we make a study to establish the minimum time associated with a good reaction rate under the optimized conditions, and the results are summarized in Figure 1.

Analyzing the Figure 1, total conversion of benzenethiol was observed after 3 h of reaction. A further decreasing of the reaction time was followed by a considerable reduction in the conversion rate of benzenethiol.

Under the optimized conditions (method A),[11] a variety of organothiols were oxidized smoothly to produce disulfides **1a–r** in

Table 2
Synthesis of disulfides according method B[a]

Entry	Time (min)	Product yield
1	15	 **1a** 98%
2	20	 **1d** 98%
3	15	 **1g** 99%
4	30	 **1j** 91%
5	20	 **1l** 97%
6	15	 **1m** 95%

[a] Yields are given for pure isolated products.

good to excellent yields (Table 1). Diphenyl disulfide **1a** was obtained in 98% isolated yield after 3 h at 60 °C (Table 1, entry 1).

Diaryl disulfides containing electron donating (Table 1, entries 2–4) and electron withdrawing groups (Table 1, entries 5–8), could be obtained in high yields. Good yields of oxidation were obtained using 2-amino-4-chlorobenzenethiol and 2-naphthalenethiol (Table 1, entries 9 and 10). Excellent yield of the disulfide was obtained with 2-mercaptobenzothiazole but this reaction was performed at 100 °C (Table 1, entry 11). Satisfactory results were achieved using benzylic or alkylic thiols yielding the corresponding disufides **1l–q** in a range of 80–99% (Table 1, entries 12–17). Additionally, the amino acid L-cysteine, which is involved in a large number of biological processes, is converted into cystine **1r** with 87% yield (Table 1, entry 18).

In order to obtain an efficient protocol in terms of energy economy, we performed these reactions under microwave irradiation. Thus, the mixture of benzenethiol (1.0 mmol) and [bmim][$SeO_2(OCH_3)$] was irradiated under stirring and fortunately, after 15 min at 30 °C, diphenyl disulfide **1a** was obtained in 98% (method B).[11] To extend the scope of method B, other organothiols were irradiated with microwaves and the corresponding disulfides shown in Table 2 were obtained in excellent yields.

Finally, a study regarding the recovering and reusing of the ionic liquid was also performed using the method B. After the total oxidation of benzenethiol, the product was extracted with petroleum ether (3 × 5 mL). The upper phase was dried and the solvent evaporated. The inferior, ionic liquid phase was dried under vacuum and reused. The selenium ionic liquid maintained its good level of oxidation activity even after being recycled four times as shown in Figure 2. The product 1a was obtained in 98%, 98%, 96%, 96%, and 94% yields after successive cycles.

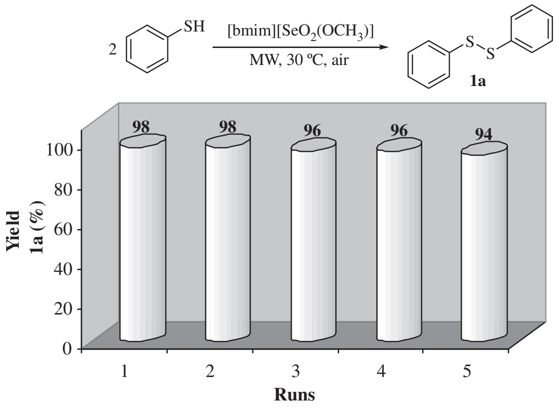


Figure 2. Reuse of [bmim][$SeO_2(OCH_3)$] under microwave irradiation.

In conclusion, [bmim][$SeO_2(OCH_3)$] has proved to be an efficient medium for the oxidation of aromatic, aliphatic, and functionalized thiols. The Se-ionic liquid acts both as solvent and catalyst and is easily recovered and utilized for further oxidation reactions. The reactions are accelerated by microwaves and the desired disulfides were obtained in good to excellent yields.

Acknowledgments

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11. *General procedure for the oxidation of thiols with [bmim][SeO$_2$(OCH$_3$)]*: Method A: In a Schlenk tube under open atmosphere and at room temperature, the corresponding thiol (1.0 mmol) was added to [bmim][SeO$_2$(OCH$_3$)][10] (1.0 mL). The reaction mixture was allowed to stir at 60 °C for the time indicated in Table 1. The progress of the reaction was monitored by TLC. Method B*:* In a 10 mL glass vial equipped with a small magnetic stirring bar, containing 1.0 mL of [bmim][SeO$_2$(OCH$_3$)] was added the thiol (1.0 mmol). The vial was tightly sealed with an aluminum/Teflon crimp top. The mixture was then irradiated in a microwave reactor (CEM Explorer) for the time indicated in Table 2 at 30 °C (temperature was measured with an IR sensor on the outer surface of the reaction vial), using an irradiation power of 100 W and pressure of 150 psi. After the reaction was complete, the product was extracted by successive washings with petroleum ether (3×5 mL), dried over MgSO$_4$, and concentrated in vacuum. The residue was purified by column chromatography on silica gel using ethyl acetate/hexanes as the eluent. *Recycle of the ionic liquid*: The aforementioned method B was used with benzenethiol (0.110 g, 1.0 mmol) and the inferior ionic liquid phase was separated and dried under vacuum. The recovered [bmim][SeO$_2$(OCH$_3$)] was used directly in the next cycle.
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