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Metal-Free Air Oxidation of Thiols in Recyclable Ionic Liquid: A Simple and Efficient Method for the Synthesis of Disulfides

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An efficient procedure for the oxidative coupling of alkyl, aryl and heteroaryl thiols with atmospheric oxygen is reported. The methodology utilizes BMIM-BF_4 as a recyclable solvent and does not require support materials or metal salts. Symmetric disulfides are obtained in excellent yields.

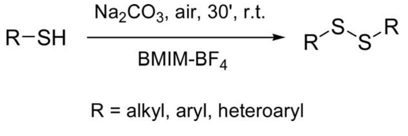
Introduction

Disulfides are a very useful class of organochalcogenium compounds with a large number of biological and chemical applications. For instance, disulfides are used as cleavable linkages in drug delivery systems,[1] have DNA cleavage properties, stabilize peptides in proteins,[2] and are responsible for the secondary and tertiary structure of proteins. In industry, disulfides have found application as vulcanizing agents and oils for rubber and elastomers.[3,4]

From a synthetic point of view, oxidative dimerization of thiols has become a routine and unmatched method for the synthesis of symmetric disulfides, mainly because a substantial number of thiols are commercially available or easily synthesized. Many elegant routes with the use of metal-based oxidizing reagents have been reported in the literature.[5–13] However, these protocols have some common disadvantages such as toxicity, costly reagents and, in some cases, low selectivity due to the over-oxidation of the final disulfide. Alternatively, the metal-free conversion of thiols to disulfides appears as an interesting option and many publications have appeared in this area.[14–20] Despite the good features, several drawbacks including instability, toxicity, high costs and laborious experimental procedures seriously restrict the usefulness of these methodologies. Therefore, a mild and environmentally harmless oxidative method for the high-yielding conversion of thiols into disulfides is still required.

In this regard, molecular oxygen (aerial oxygen or neat oxygen under pressure) is known to be an inexpensive, easy to handle and scarcely toxic reagent for the oxidation of thiols to disulfides.[21] Ruano et al.[22] have recently reported an efficient system in which thiols are oxidized by atmospheric oxygen in DMF/Et_3N under sonication. However, the main drawback of this method is the non-reuse of the solvent, since DMF is eliminated after the reaction work-up.

In recent years, more attention has been paid to the development of new synthetic methods using ionic liquids due to their unique chemical and physical properties, such as excellent chemical and thermal stability with ease of reuse, low vapor pressure and non-flammability.[23] They have been employed as an alternative solvent media for a broad range of different chemical transformations.[24–31] It is known that the use of polar-aprotic solvents with high dielectric constants favors the oxidation of thiols with oxygen.[21,22] Thus, the use of imidazolium ionic liquids constitutes an interesting alternative for this reaction,[32] since they gather the desirable characteristics to the solvent with the condition of an environmentally benign compound. Chauhan and co-workers[33] reported a biomimetic oxidation of thiols with molecular oxygen in BMIM-BF_4, but in this case an additional oxidant species [cobalt(II) phthalocyanines] was required. In line with our current interest in the synthesis and applications of organochalcogen compounds[34] along with the development of the organochalcogenium chemistry in ionic liquids,[35] we report herein an efficient metal-free oxidation of thiols using aerial oxygen in BMIM-BF_4 as a reusable solvent (Scheme 1). The study resulted in a mild, inexpensive and broadly applicable methodology for the synthesis of symmetrical disulfides.



Scheme 1.

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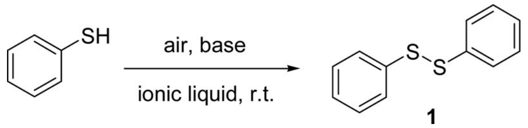
Results and Discussion

Aiming to determine the optimum conditions, we performed studies on the role of different factors that can influence the coupling reaction. The results are collected in Table 1. In a standard protocol, the reaction was conducted employing thiophenol as a representative thiol with 1.0 equiv. of Et_3N at room temperature with the bubbling of air.[36]

Table 1. Optimization of the reaction conditions for the oxidative coupling of thiophenol in ionic liquids.



1

Entry	Ionic liquid	Base	Time [min]	Yield[a] [%]
1	BMIM-BF_4	Et_3N	45	93
2	BMIM-OTf	Et_3N	45	90
3	BMIM-PF_6	Et_3N	45	92
4	BMIM-BF_4	Et_3N	30	92
5	BMIM-BF_4	Et_3N	20	68
6	BMIM-BF_4	pyridine	30	84
7	BMIM-BF_4	K_2CO_3	30	96
8	BMIM-BF_4	Cs_2CO_3	30	95
9	BMIM-BF_4	KOH	30	99
10	BMIM-BF_4	Na_2CO_3	30	99
11	BMIM-BF_4	Na_2CO_3	60	43
12	BMIM-BF_4	–	60	traces
13	BMIM-BF_4	Na_2CO_3	30	94

[a] Yields were determined by GC. [b] 0.5 equiv. of Na_2CO_3 was used. [c] This reaction has been performed with 10 g (0.069 mol) of thiophenol.

In a first set of experiments, the influence of different ionic liquids was studied. It was verified that most of the different anions had no significant effect on the course of the reaction, giving the desired product in yields ranging from 90 to 93% (Table 1, Entries 1–3). Nevertheless, BMIM-BF_4 was slightly more efficient (entry 1) and was chosen as the standard ionic liquid in further optimizations.

Attempting to obtain an efficient methodology in terms of energy economy, we turned our attention to establishing the minimum time associated with a good reaction rate. Figure 1 shows a typical plot of GC yield vs. time for this reaction. Fortunately, no significant decrease in the yield was observed when reducing the reaction time from 45 to 30 min (compare entries 1 and 4, Table 1). However, a further decrease in the reaction time was followed by a considerable decrease in the conversion rate (entry 5).

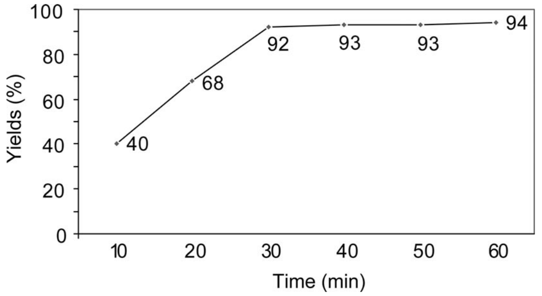


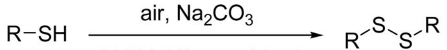
Figure 1. Plot of GC yield vs. time for the oxidation of thiophenol in BMIM-BF_4.

The influence of the different bases was the next parameter studied. In this context, a number of organic (entries 4 and 6, Table 1) and inorganic (Entries 7–10) bases could be used to afford diphenyl disulfide in high yields. Notably, KOH and Na_2CO_3 obtained the best performances among the screened bases, furnishing the desired product in almost quantitative yield (Entries 9 and 10, respectively). As a result, Na_2CO_3 was selected as the optimum base because of its greener nature and lower cost in comparison with KOH, besides the mildness of the process. The use of a lower amount of Na_2CO_3 resulted in a considerable decrease in the conversion even when the reaction time was increased (see entry 11). This finding supports the conversion of thiol to thiolate as a step prior to its coupling to form disulfide.[37]

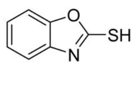
Finally, diphenyl disulfide was prepared in multigram scale without losing of the good features (Table 1, entry 13). This find suggests that the present method is suitable for application in larger-scale processes.

Using the optimized conditions,[38] the present reaction was further expanded to a broader range of thiols in order to evaluate the scope and limitations of the method. As can be observed in Table 2, the electronic effects in aromatic

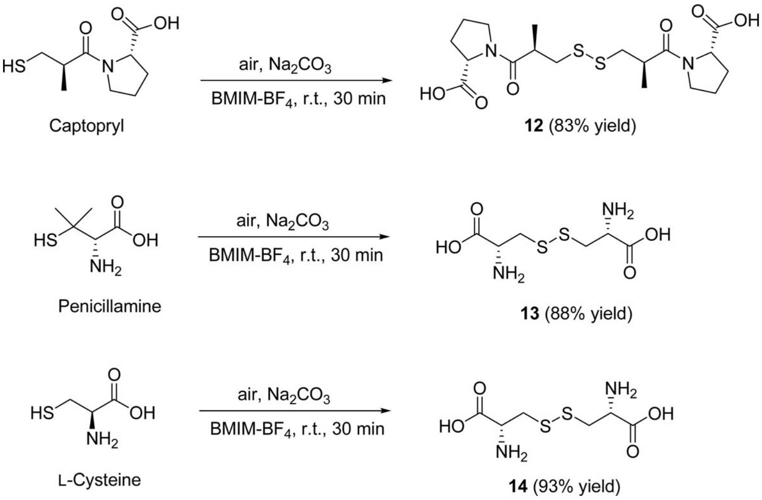
Table 2. Oxidation coupling of thiols in BMIM-BF_4.



1–11

Entry	Thiol	Product	Yield[a]	M.p./b.p. (°C)[Lit.]
1	PhSH	**1**	99	57–58 [59–60][39]
2	*p*-MeC_6H_4SH	**2**	95	51–53 [52–56][40]
3	*p*-$MeOC_6H_4SH$	**3**	97	42–43 [43–44][8b]
4	*p*-ClC_6H_4SH	**4**	94	72–74 [73–74][41]
5	*o*-ClC_6H_4SH	**5**	92	89–90 [88–90][40]
6	2-mercaptopyridine	**6**	90	56–57 [57–58][40]
7		**7**	87	110–112 [112–113][42]
8	*n*-C_3H_7SH	**8**	89	195 [194][43]
9	*n*-$C_{12}H_{25}SH$	**9**	84	30–32 [32][44]
10	$PhCH_2SH$	**10**	97	69–70 [70–71][40]
11	*t*BuSH	**11**	83	198 [200][20]

[a] Yields relating to pure isolated products, characterized by ^1H and ^{13}C NMR spectroscopic data.



Scheme 2.

thiols do not play a significant role in terms of conversion to the desired product (Entries 2–5). For instance, bis(4-methoxyphenyl) disulfide containing an electron-donating group and bis(4-chlorophenyl) disulfide containing an electron-withdrawing group were obtained in 97% and 94% yield, respectively (entries 3 and 4). Additionally, thiols derived from aromatic heterocycles could also be employed under these conditions to afford the respective disulfides in excellent yields (entries 6 and 7). Finally, aliphatic thiols were oxidized to give the corresponding disulfides in very good yields (Table 2, entries 8–11).

As a further extension, thiols with more complex side chains were employed to provide a series of disulfides bearing interesting functionalities. Moreover, the organochalcogenides selected to perform these tests are important bioactive compounds. In this regard, captopryl,[44] penicillamine[45] and L-cysteine[2] were allowed to react under the standard conditions,[46] and the results were very encouraging with good yields of the respective disulfides being obtained (Scheme 2). These findings strongly suggest that the current methodology is suitable for a broader range of applications, since basic (amine) or acidic (carboxylic acid) side chains can be tolerated.

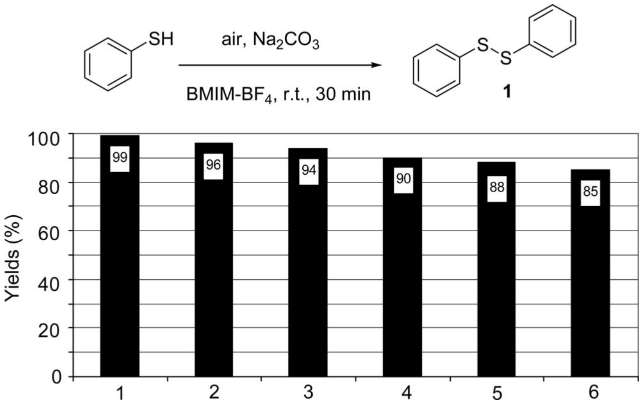


Figure 2. Reuse of BMIM-BF$_4$.

The issue of developing economically attractive and environmentally friendly methods is one of our prime concerns. This prompted us to evaluate the possibility of recycling the ionic liquid employed in our reactions. After the work-up, the recovered BMIM-BF$_4$[47] was reused for further 5 experiments, with a reasonable decrease in the yield of diphenyl disulfide in each cycles (see Figure 2). We attribute this diminishing to a partial decomposition of BMIM-BF$_4$, since it is known that the 2-position of imidazolium cation can be deprotonated even under modestly basic conditions,[48] leading to the formation of Arduengo-type carbenes.[49]

Conclusions

In conclusion, we have developed a practical and efficient procedure for the oxidative coupling of thiols in reusable BMIM-BF$_4$ with aerial oxygen in the absence of metal catalysts. The method is applicable to a wide variety of thiols, providing structurally diverse disulfides in high yields. Most importantly, the present protocol offers significant improvements with regard to operational simplicity, green character and low costs, representing a useful alternative to the existing methodologies.

Acknowledgments

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[38] General procedure for the synthesis of disulfides **1**–**11** (Table 2): in a Schlenk tube under open atmosphere and at room temperature, the corresponding thiol (1.0 mmol) and Na_2CO_3 (1.0 mmol) were added to BMIM-BF_4 (1.0 mL), and aerial oxygen was bubbled into the reaction mixture with stirring. The progress of the reaction was monitored by TLC. After the reaction was complete, the product was extracted by successive washings with diethyl ether (5 × 5 mL) and drying over $MgSO_4$. The solvent and volatiles were completely removed under vacuum to give the crude product. The compounds were purified by column chromatography over silica gel.

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[46] General procedure for the synthesis of disulfides **12**–**14** (Scheme 2): In an open Schlenk tube and at room temperature, the corresponding thiol (1.0 mmol) and Na_2CO_3 (2.0 mmol) were added in BMIM-BF_4 (1.5 mL), and aerial oxygen was bubbled through the reaction mixture wile stirring for 30 min. After the reaction was complete, the mixture was extracted with DCM (20 mL) and H_2O (2 × 10 mL), to separate the disulfides in the aqueous layer and BMIM-BF_4 in DCM. Products **12**–**14** were recrystallized from water.

[47] After work-up, BMIM-BF_4 was treated with DCM and filtered through celite to remove the residues. The solution was dried with $MgSO_4$ and the volatile components were removed under vacuum. The recovered ionic liquid was reused in subsequent reactions.

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