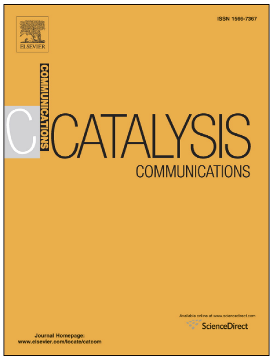

Laccase-catalyzed in situ generation and regeneration of N-phenyltriazolinedione for the aerobic oxidative homo-coupling of thiols to disulfides

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Laccase-catalyzed *in situ* generation and regeneration of *N*-phenyltriazolinedione for the aerobic oxidative homo-coupling of thiols to disulfides

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Abstract

The first report on aerobic *in situ* generation and regeneration of *N*-phenyltriazolinedione, a valuable oxidizing agent, from a catalytic amount of *N*-phenyl urazole in the presence of a laccase enzyme is presented. The application of a 4-phenyl urazole/Laccase/O_2 as a new cooperative catalytic oxidation system is reported for a transition-metal-free and halogen free oxidative homo-coupling reaction of structurally diverse thiols to their corresponding disulfides with good to excellent yields in a phosphate buffer solution under mild reaction conditions.

Keywords: Laccase enzyme, 4-Phenyl urazole, Cooperative catalytic system, *N*-phenyltriazolinedione, Aerobic oxidative, Disulfides

1. Introduction

Disulfides have a vital role in different fields such as: vulcanizing agents in industry, efficacious agents in folding and stability of the proteins as well as their performance in biochemistry, pharmaceutical activity and significant synthetic intermediates in organic synthesis [1-2]. These applications can reflect the importance of thiols oxidative coupling to their corresponding disulfides. Many oxidizing reagents have been reported in the literature to accomplish this transformation [3-13]. However, these reagents show poor atom efficiency and are often toxic. There is substantial interest towards the use of molecular oxygen or air as the highly atom-economical, environmentally benign, and abundant oxidant in the oxidative coupling of thiols in the presence of catalysts. Accordingly, various catalysts such as cobalt-phthalocyanine [14], gold [15] and heterocyclic bismuth (III) compounds [16] have been used for the oxidation of thiols using molecular oxygen as terminal oxidant. Although these methods have been developed considerably, these procedures suffer from some problems such as low catalytic efficiency, tedious catalyst preparation and the use of toxic organic solvents. In addition, they may possibly leave toxic traces of heavy metals in the products. Therefore, it is a purpose for chemists to gain more effective, non-metallic and environmentally benign replacements.

4-Substituted 1,2,4-triazole-3,5-diones are notable for their ability to participate in a wide range of concerted and stepwise reactions [17]. Also, they were introduced as one of the efficient oxidative reagents due to its dehydrogenating feature [18-21]. Despite the versatility of triazolediones, their low stability, high cost and relatively high toxicity and also challenges that can arise in removing their reduced forms from the reaction products when used as stoichiometric oxidant are disadvantages that could limit using of them in green organic reactions. In order to avoid the abovementioned disadvantages, the best strategy is the *in situ* generation of these valuable intermediates and organic oxidizing agents from the oxidation of their corresponding urazoles that are stable, commercially available and cheap compounds. Although various reagents have been reported for the oxidation of urazoles to the corresponding triazolindiones (TADs) [22-25], these procedures suffer from one or more disadvantages such as harsh conditions, the use of toxic and expensive stoichiometric reagents and the production of large quantities of waste.

From the viewpoint of green and sustainable chemistry, O_2 and air are highly atom-economical, environmentally benign, and abundant oxidant that minimize the generation of hazardous materials. Therefore, there is substantial interest towards the use of molecular oxygen or air as terminal oxidant. Direct aerobic oxidation of urazoles to the corresponding triazolindiones is typically not feasible. In reality, a catalyst must be employed for aerobic oxidation of urazoles with molecular oxygen. The employing of enzymes as safe and biodegradable catalysts offer many benefits since biocatalytic reactions can be performed under mild conditions [26-27]. In this context, the oxidative coupling of the various organic compounds using aerial oxygen has been catalyzed by a laccase enzyme [28-29] (benzendiol; O_2 oxidoreductase, E.C. 1.10.3.2.). Higher redox potentials could be reached using laccase and different cooperative agents to embrace the oxidation of diverse functional groups such as alcohols, ethers and amines [30-32]. Recently, Beifuss and co-worker have reported metal-free aerobic oxidative coupling of heterocyclic thiols using a laccase mediator system (LMS) [33]. Although, this finding presented an interesting breakthrough in the field of metal-free aerobic oxidation of thiols, this method requiers a large amount of laccase and the use of mediators that are quite expensive and relatively toxic. Therefore, the discover of new cooperative catalytic systems of laccase and cheap, commercially available in large quantities, shelf-stable and active organic mediators for aerobic oxidation of thiols and other organic compounds is in demand.

2. Experimental

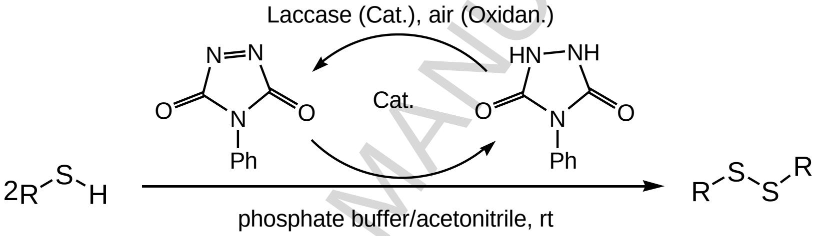
The activity assays of commercial enzyme laccase from T. versicolor: The activity of laccase was determined spectrophotometrically with 2,2'-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS, $\varepsilon = 36\ 000\ M^{-1}.cm^{-1}$) as substrate (5 mM, 100 µL) in acetate buffer (100 mM, pH=5.0). The absorbance change was observed at 420 nm for 5 min at room temperature [34]. One unit of activity is defined as the amount of enzyme required to oxidize 1 µmol of ABTS per minute. The activity of laccase enzyme batch applied in this investigation was evaluated at 0.87 U/mg.

General procedure for aerobic oxidation of sulfides to their corresponding disulfide in the presence of laccase/4-phenyl urazole cooperative catalyst system

To a solution of 1 mmol of thiol in acetonitrile (2 mL), was added a solution of 8 mL of phosphate buffer including laccase (40 U) and 4-phenyl urazole (10 mol%). The resulting mixture was stirred under air at room temperature for the time specified. After completion of the reaction (monitored by TLC), NaOH (10%, 10 mL) was added and the mixture was stirred for 5 min. The products were extracted with diethyl ether (3 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude products were purified by recrystallization or chromatography on silica gel (*n*-hexane/EtOAc, 5/1). All the products were known and characterized by comparison of their spectral data (^{1}H NMR) and physical properties (melting point) with those of authentic samples.

3. Results and discussions

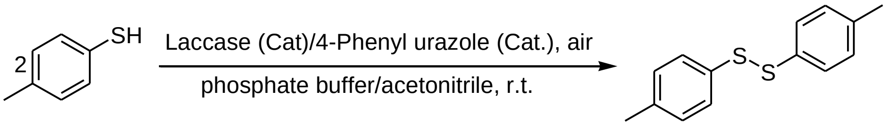
Very recently we have used a laccase enzyme as green catalyst to mediate aerobic oxidation of urazoles to triazolindiones as valuable intermediate for the synthesis of 4-arylsulfonyl urazoles [35]. Inspired by the successful results in this work and the ability of triazolinediones to act as an effective stoichiometric oxidant for organic compounds [18-21], herein, we want to present for the first time aerobic *in situ* generation and regeneration of 4-phenyl triazoledione from a catalytic amount of 4-phenyl urazole in the presence of laccase as biocatalyst for the oxidation of thiols in phosphate buffer/acetonitrile mixture at room temperature (Scheme 1).



Scheme 1. Aerobic oxidative coupling of thiol to disulfide catalyzed by a laccase/4-phenyl urazole cooperative system

In order to optimize the reaction conditions, the aerobic oxidative coupling of 4-methyl thiophenol was selected as a model reaction. Initially, oxidation of 4-methyl thiophenol was conducted in the presence of laccase (40 U) as catalyst and air as an oxidant in MeCN/NaPBS mixture (2:8) as solvent at room temperature for 3h. Under these conditions, low conversion of 4-methyl thiophenol was observed (Table 1, entry 1). When the amount of laccase was increased to 200 U, the reaction was completed after 24h (Table 1, entry 3). In order to reduce the amount of laccase used and the reaction time, 4-phenyl urazole was used as mediator. Upon further investigation (Table 1, entries 4-8), 40 U of laccase and 0.1 mmol of 4-phenyl urazole were selected as standard concentrations in all further reactions. The oxidative coupling reaction of 4-methyl thiophenol in water, ethanol, water/ethanol (1/1; v/v), THF and THF/water (1/1; v/v) media are proceeded with moderate yields ranging from 37%-55% (entries 10-14).

Table 1. Optimization of the reaction conditions with respect to the effect of concentration of laccase and 4-phenyl urazole and solvent on aerobic oxidative coupling of 4-methyl thiophenol[a]

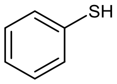
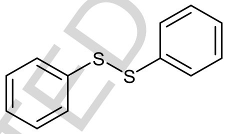
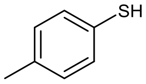
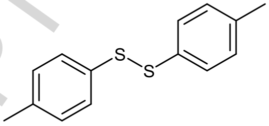
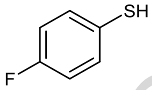
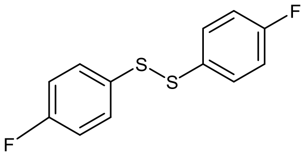
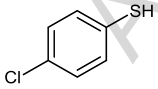
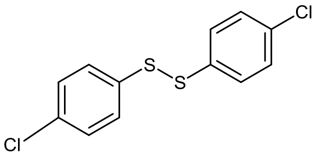
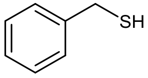
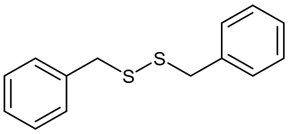
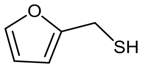
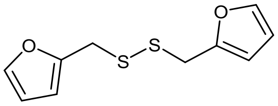


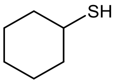
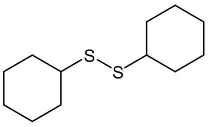
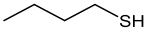
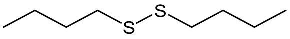
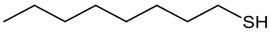
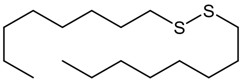
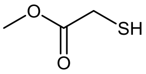
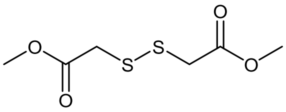
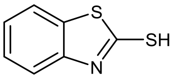
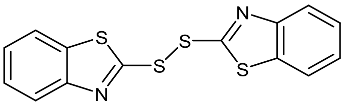
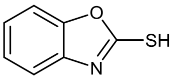
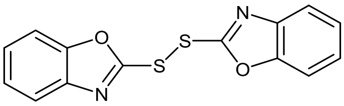
Entry	Solvent	Laccase (U)	4-Phenyl urazole (mmol)	Time (h)	GC Yield (%)
1	MeCN/NaPBS	40	-	3	45
2	MeCN/NaPBS	100	-	3	75
3	MeCN/NaPBS	200		24	100
4	MeCN/NaPBS	100	0.05	5	100
5	MeCN/NaPBS	100	0.1	1.5	100
6	MeCN/NaPBS	40	0.05	3	60
7	**MeCN/NaPBS**	**40**	**0.1**	**3**	**100**[b]
8	MeCN/NaPBS	40	0.2	3	100
9	MeCN/NaPBS	-	0.2	3	45
10	Water	40	0.1	3	37
11	Ethanol	40	0.1	3	45
12	Water/Ethanol (1:1)	40	0.1	3	50
13	THF	40	0.1	3	55
14	Water/THF (1:1)	40	0.1	3	55

[a] Reaction conditions: 4-methyl thiophenol (1 mmol), phosphate buffer (0.1 M, 8 mL, pH = 5.0), acetonitrile (2 mL), air, rt, [b] Selected reaction conditions.

Encouraged by the initial success, the generality and applicability of this method was further examined for aerobic oxidative coupling of various thiols including aromatic (with electron-withdrawing and electron-releasing groups), benzylic, heterocyclic and aliphatic (cyclic and acyclic) thiols (Table 2).

Table 2. Aerobic oxidative coupling of thiols to disulfides catalyzed by laccase/4-phenyl urazole system[a]

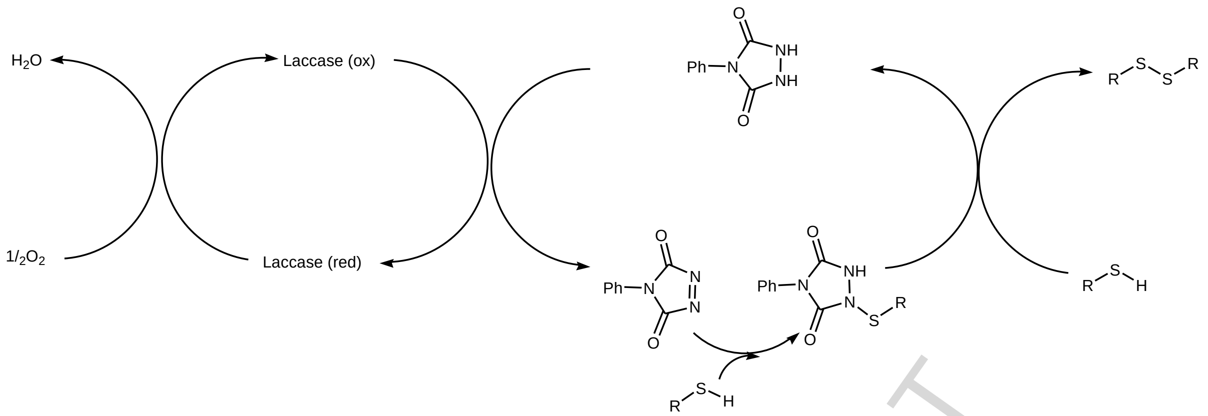
Entry	Thiol	Disulfide	Time (h)	Yield (%)[b]	M. p. (°C)	M. p. (°C) [Lit.]
1			4	95	60-61	61-62 [3]
2			3	95	39-40	39-42 [4]
3			5	92	Oil	Oil [9]
4			6	95	69-71	70-72 [6]
5			7	90	69-70	69-70 [5]
6			10	85	Oil	Oil [6]

7			13	85	123-124	125-128 [7]
8			9	87	Oil	Oil [8]
9			10	88	Oil	Oil [6]
10			12	85	Oil	Oil [10]
11			14	75	176-178	177-180 [4]
12			15	75	84-86	84-88 [4]

[a]Reaction conditions: Laccase (40 U), thiol (1 mmol), 4-phenyl urazole (0.1 mmol), phosphate buffer (0.1 M, 8 mL, pH = 5.0), acetonitrile (2 mL), air, rt. [b]Isolated yield.

As shown in Table 2, the corresponding disulfides were obtained in good to high yields, it seems that the resulting yields for oxidative coupling of aromatic thiols are slightly higher in comparison with aliphatic thiols. It was shown that aromatic thiols oxidized more quickly than aliphatic thiols. It is also observed that aromatic thiols with electron-donating groups (Entry 2) are more reactive than thiols with electron-withdrawing groups (Entries 3, 4). Interestingly, 2-mercaptobenzothiazole and 2-mercaptobenzimidazole which are relatively unreactive thiols were also converted to the corresponding disulfides in good yields under the same reaction conditions (Table 2, entries 11-12).

Although the exact mechanism of this reaction is not clear, based on previously reported mechanisms about application of laccase in oxidation of catechol in tandem reactions [29-33, 35] and oxidative coupling of thiols using 4-phenyl-1,2,4-triazole-3,5-dione as stoichiometric oxidant [20], the proposed mechanism and catalytic cycle for the aerobic oxidative coupling reaction of thiol to corresponding disulfide in the presence of the laccase-urazole cooperative catalyst system has been depicted in Scheme 2. It is supposed that the reaction begins with the oxidation conversion of 4-phenyl urazole to 4-phenyl-1,2,4-triazole-3,5-dione by laccase that is accompanied by the reduction of oxygen to water. Then, the oxidative coupling reaction of thiol leads to the formation of disulfide that is motivated by the reduction conversion of 4-phenyl-1,2,4-triazole-3,5-dione to 4-phenyl urazole.



Scheme 2. Proposed mechanism and catalytic cycle for the aerobic oxidation

4. Conclusion

In summary, we have found the simple, green and efficient method for aerobic oxidative coupling of structurally diverse thiols to their corresponding disulfides in the presence of laccase/4-phenyl urazole as a novel cooperative catalytic system in phosphate buffer (pH = 5.0)/ acetonitrile solution at room temperature. This present method is more eco-friendly and practical than other currently available methods due to being free from any transition metal and halide and the quantitative conversion under mild reaction conditions. Further studies on the scope and synthetic application of this new cooperative catalyst system are in progress in our laboratory.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at.

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Graphical Abstract

Laccase-catalyzed in situ generation and regeneration of *N*-phenyltriazolinedione for the aerobic oxidative homo-coupling of thiols to disulfides

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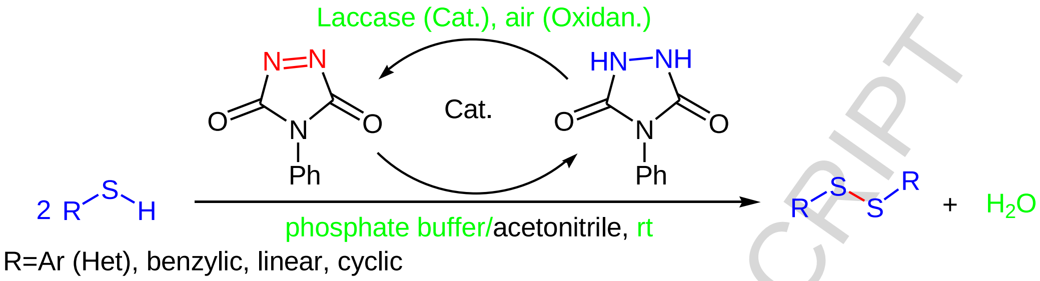

Highlights

- Aerobic in situ generation and regeneration of *N*-phenyltriazolinedione catalyzed by laccase
- Discovering a new cooperative catalytic system consisting of laccase and 4-phenyl urazole
- The first report application of a laccase/4-phenyl urazole for the aerobic oxidation of thiols
- This catalyst system allows for greener methodology that affords high reaction yields.