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Laccase-catalyzed, aerobic oxidative coupling of 4-substituted urazoles with sodium arylsulfinates: green and mild procedure for the synthesis of arylsulfonyl triazolidinediones

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ABSTRACT

The direct aerobic oxidation of 4-substituted urazoles using the laccase enzyme from Trametes versicolor in a phosphate buffer solution at ambient temperature, and subsequent cross-coupling with sodium benzenesulfinates was investigated to afford arylsulfonyl-1,2,4-triazolidine-3,5-dione derivatives in good to high yields.

Keywords: 4-substituted urazole, sodium benzenesulfinate, laccase enzyme, aerobic oxidation, arylsulfonyl triazolidindione

1. Introduction

Laccases (benzenediol: oxygen oxidoreductase, EC 1.10.3.2) belong to a group of polyphenol oxidases containing copper atoms in the catalytic center. These multicopper oxidases catalyze oxidation reactions using atmospheric oxygen as the oxidant and produce water as the only by-product. For example, Ragauskas and co-workers reported the biocatalytic synthesis of phenothiazones and related compounds in an aqueous system under mild conditions using laccase oxidation.[1] Beifuss and co-workers reported various laccase-catalyzed domino and oxidation reactions.[2-6] Kidwai and co-workers investigated the enzymatic laccase oxidation of catechols/hydroquinones in the presence of Meldrum's acid as a nucleophile in an aqueous solution.[7] Kragl and co-workers investigated the application of the fungal laccase from Myceliophthorathermophila (Novozym®51003) for the oxidative C-C coupling of phenolic compounds.[8]

4-Substituted-1,2,4-triazolidine-3,5-dione derivatives are notable for their ability to participate in a wide range of concerted and stepwise reactions.[9-11] For example, the oxidation of urazoles represents one of the best strategies for the preparation of these valuable intermediates. Several reagents have been reported for this key transformation, including Ph_3BiCO_3,[12] periodic acid/$NaNO_2$,[13] silica sulfuric acid/$NaNO_2$,[14] trichloroisocyanuric acid,[15] silica chloride/ $NaNO_2$,[16] HNO_3,[17] N_2O_4,[18] chlorine or bromine,[19] $Ca(OCl)_2$,[20] $K_2Cr_2O_7/AlCl_3$,[21] and *p*-toluenesulfonyl isocyanate/DMSO.[22] However, these methods have disadvantages including harsh reaction conditions, poor atom efficiency, the use of toxic and gaseous reagents, and the production of large quantities of waste. Thus, from the viewpoint of green and sustainable chemistry, there is significant motivation to develop both cleaner and milder methods for the oxidation of urazoles to the corresponding triazolidindiones (TADs).

Although the direct laccase catalyzed, aerobic oxidation of a broad range of substrates, including mono-, di-, and polyphenols, aminophenols, methoxyphenols and aromatic amines, have been studied,[23,24] to the best

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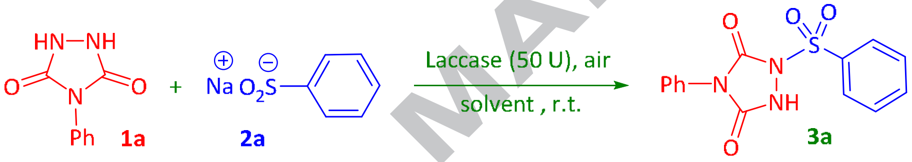
of our knowledge there are no reports regarding the use of laccase for the aerobic oxidation of urazoles to TADs. Therefore, in continuation of our studies on applications of the laccase enzyme in organic synthesis,[25,26] herein we disclose the use of laccase from *Trametes versicolor* as a biocatalyst for the synthesis of arylsulfonyl-1,2,4-triazolidine-3,5-dione derivatives *via* the direct aerobic oxidative coupling reaction between 4-substituted urazole derivatives and sodium arylsulfinates in a phosphate buffer solution (PBS) using air as an oxidant.

2. Results and Discussion

The laccase catalyzed, aerobic oxidative coupling reaction of 4-phenylurazole **1a** with sodium benzenesulfinate **2a** was initially examined in aqueous media and a range of organic solvents (Table 1), where it was determined that PBS (0.1 M, pH = 5.0) was optimal (Entry 3). In water, ethanol and water/ethanol (1:1), the reaction proceeded with moderate yields (40-57%; entries 8-10). No reaction took place in MeCN, DMF and DMSO, probably due to denaturation of the laccase enzyme (Entries 11-13).

Table 1. Solvent optimization for the synthesis of phenylsulfonyl triazolidinedione **3a**[a]



Entry	Solvent	GC Yield **3a** (%)[b]
1	PBS (0.1 M, pH = 7.0)	82
2	PBS (0.1 M, pH = 6.0)	75
3	PBS (0.1 M, pH = 5.0)	>99
4	PBS (0.1 M, pH = 4.0)	77
5	acetate buffer solution (0.1 M, pH = 5.0)	65
6	phosphate/citrate buffer solution (0.1 M, pH = 7.0)	57
7	phosphate/citrate buffer solution (0.1 M pH = 5.0)	50
8	H_2O	40
9	EtOH	52
10	H_2O/EtOH (1:1)	57
11	MeCN	-
12	DMF	-
13	DMSO	-

[a] Reagents and conditions: laccase (57.5 mg, 50 U), **1a** (1.0 mmol), **2a** (1.0 mmol), solvent (10 mL), air, r.t., 4 h.
[b] GC yield.

The effect of the laccase amount on the reaction rate was also studied (Table 2). A blank reaction was carried out to determine the catalytic effectiveness of laccase; no product formation occurred even after 20 h

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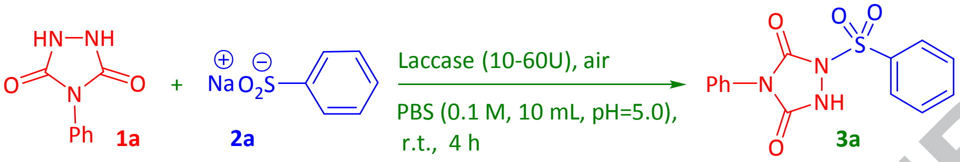
(Entry 7). The rate of product formation was enhanced with increasing catalyst amount, and the optimum enzyme concentration was found to be 50 U (Entry 5).

Table 2. Optimization of the amount of laccase for the synthesis of phenylsulfonyl triazolidinedione **3a**[a]



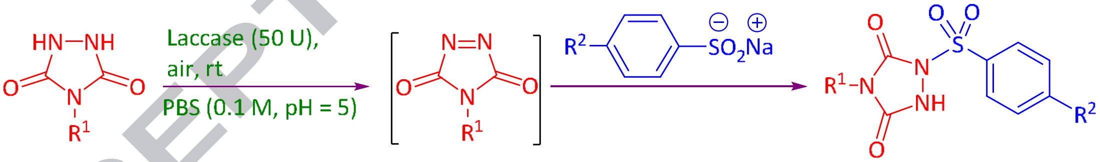
Entry	Laccase amount (U)	GC Yield **3a** (%)[b]
1	10	21
2	20	50
3	30	70
4	40	85
5	50	>99%
6	60	>99%
7	-	-

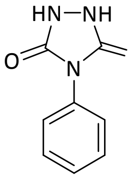
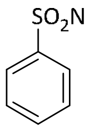
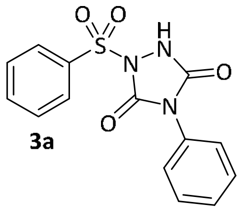
[a] Reagents and conditions: laccase (10-60 U), **1a** (1.0 mmol), **2a** (1.0 mmol), PBS (0.1 M, 10 mL, pH=5.0), air r.t., 4 h.
[b] GC yield

Finally, the effect of reaction temperature was investigated using various temperatures ranging from 25 °C to 65 °C; the optimum temperature found to be the room temperature (25 °C).

The scope of the aerobic oxidative coupling reaction between various urazole derivatives and sodium arylsulfinates (Table 3) were examined using the optimized conditions: laccase (57.5 mg, 50 U) in PBS (0.1 M, 10 mL, pH = 5.0) at room temperature.

Table 3. Synthesis of various arylsulfonyl triazolidinedione derivatives[a]



Entry	Urazole	Sodium arylsulfinate	Products	Time (h)	Yield (%)[b]
1	 **1a**	 **2a**	 **3a**	4	95

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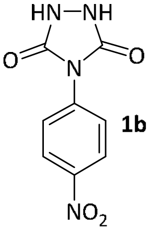
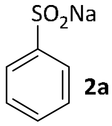
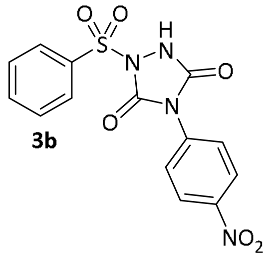
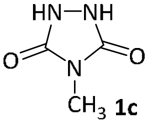
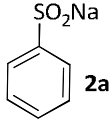
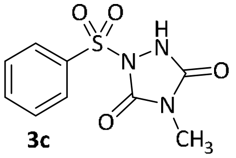
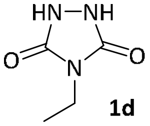
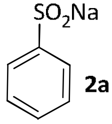
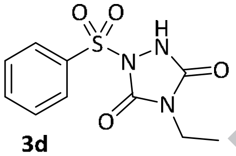
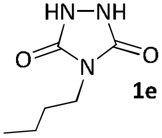
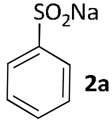
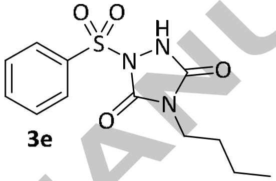
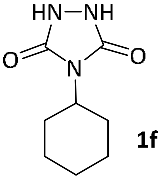
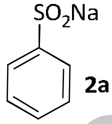
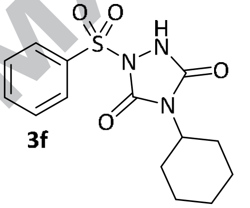
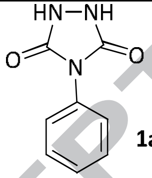
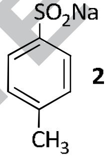
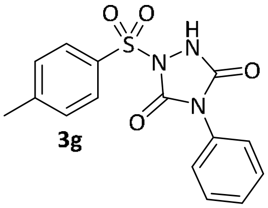
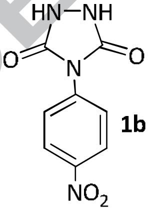
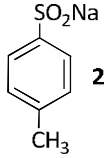
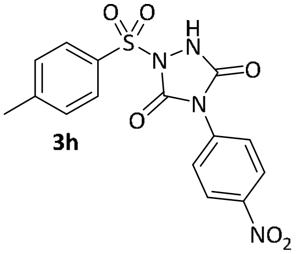
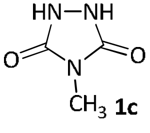
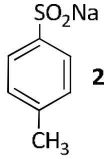
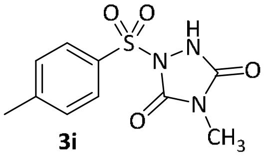
2	 **1b**	 **2a**	 **3b**	6	88
3	 **1c**	 **2a**	 **3c**	2	92
4	 **1d**	 **2a**	 **3d**	2	95
5	 **1e**	 **2a**	 **3e**	2	95
6	 **1f**	 **2a**	 **3f**	3	97
7	 **1a**	 **2b**	 **3g**	3.5	87
8	 **1b**	 **2b**	 **3h**	5.5	85
9	 **1c**	 **2b**	 **3i**	2	93

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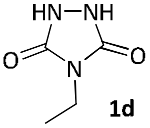
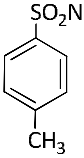
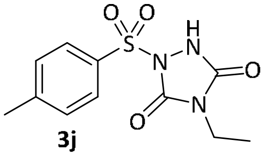
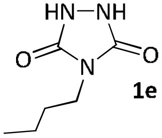
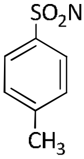
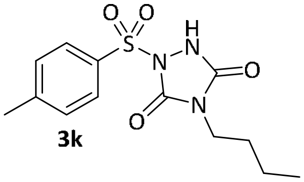
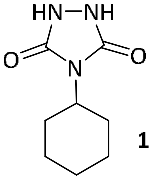
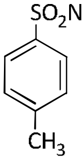
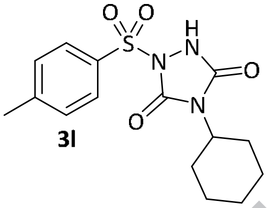
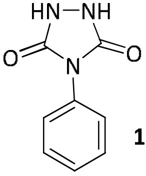
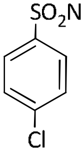
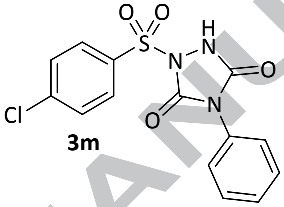
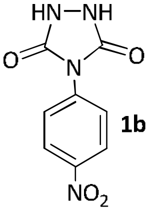
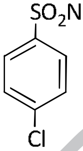
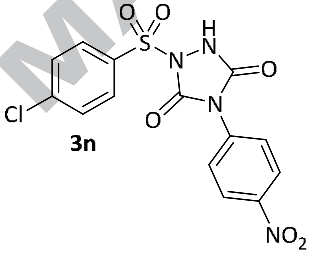
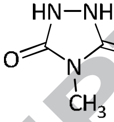
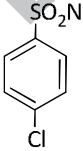
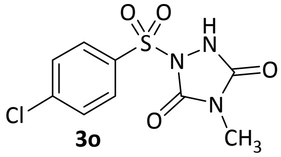
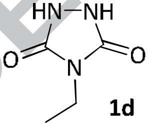
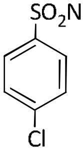
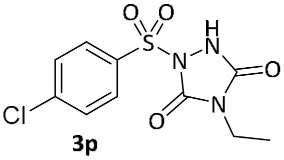
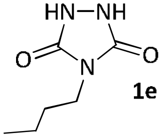
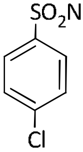
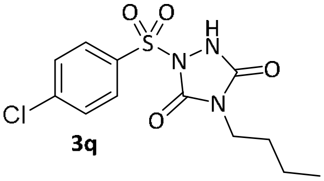
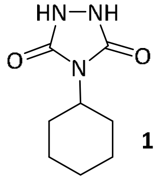
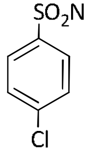
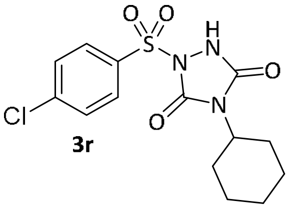
10	 **1d**	 **2b**	 **3j**	2	90
11	 **1e**	 **2b**	 **3k**	2	96
12	 **1f**	 **2b**	 **3l**	2.5	97
13	 **1a**	 **2c**	 **3m**	5	86
14	 **1b**	 **2c**	 **3n**	7	87
15	 **1c**	 **2c**	 **3o**	2.5	93
16	 **1d**	 **2c**	 **3p**	2.6	87
17	 **1e**	 **2c**	 **3q**	2.5	92

18	 **1f**	 **2c**	 **3r**	4	89

[a] Reagents and conditions: laccase (57.5 mg, 50 U), **1a-f** (1 mmol), **2a-c** (1 mmol), PBS (0.1 M, 10 mL, pH=5.0), air, r.t., 4 h.
[b] Isolated yield

The laccase catalyzed, aerobic oxidative coupling reaction between similar aza-heterocyclic compounds, such as phthalhydrazide and succinic hydrazide, with sodium phenyl sulfinate under various reaction conditions did not give the desired products and the starting materials remained intact.

The greenness of this method was compared with previously reported methods for the oxidation of urazoles (ESI, Table S1). In contrast to the reported procedures, the laccase/air system has attractive features including mild conditions, the use of laccase as a biodegradable catalyst which is derived from renewable resources, and an environmentally compatible solvent.

3. Conclusion

In summary, we have reported the synthesis of a range of 1-sulfonyl-1,2,4-triazolidine-3,5-dione derivatives *via* the aerobic oxidative coupling of 4-substituted urazoles with sodium arylsulfinates in good to high yields, using air as a terminal oxidant and laccase as an eco-friendly biocatalyst in PBS as a green solvent.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/....

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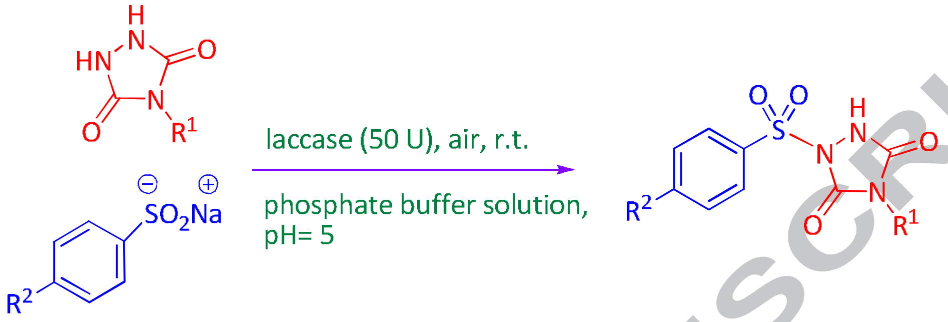
Laccase-catalyzed, aerobic oxidative coupling of 4-substituted urazoles with sodium arylsulfinates: green and mild procedure for the synthesis of sulfonyl triazolidinediones

Abdollah Rahimi,[a] Davood Habibi,*[a] Amin Rostami,*[b] Mohammad Ali Zolfigol,[a] Shadpour Mallakpour[c]



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Revised Highlights

1. Direct oxidation of 4-substituted urazoles by laccase enzyme from Trametes versicolor.
2. Cross-coupling reaction of oxidized form of urazoles with sodium benzenesulfinates.
3. Synthesis of arylsulfonyl-1,2,4-triazolidine-3,5-dione derivatives.
4. The use of air as an eco-friendly oxidant.
5. Working in green conditions (aqueous media and ambient temperature).

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