Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201400103

Synthesis of Quinazolinones from Alcohols *via* Laccase-Mediated Tandem Oxidation

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Received: January 27, 2014; Revised: March 8, 2014; Published online: ■■ ■■, 0000

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201400103.

Abstract: This paper describes the synthesis of quinazolinones *via* a tandem reaction using the laccase-mediator system under mild conditions. The procedure involved the laccase-catalyzed oxidation of alcohols to the corresponding aldehydes, followed by cyclocondensation with isatoic anhydride and a number of amines to afford 2,3-dihydroquinazolin-4(1*H*)-ones, which were further oxidized to quinazolinones in useful yields. The use of an enzyme as the catalyst, O_2 as an environmentally friendly oxidant, and a citrate buffer as the green solvent represents a novel and efficient approach for the one-pot synthesis of quinazolinones.

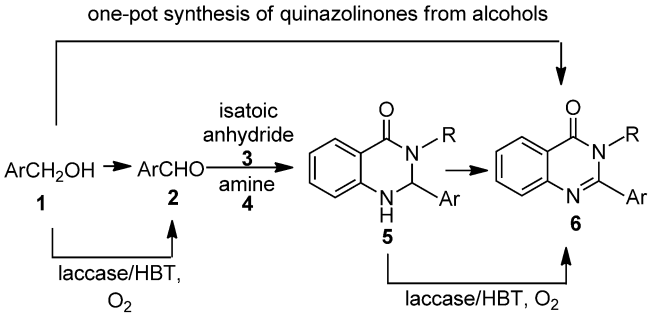
Keywords: biocatalysis; laccase; oxidation; oxidoreductases; quinazolinones

Introduction

The development of green processes, such as employing safe catalysts, waste minimization, replacing toxic solvents with H_2O, and using O_2 as an environmentally benign oxidant, in the chemical industry has gained significant attention in recent years.[1] Within this context, biocatalysts, as safe catalysts in chemical and pharmaceutical industries, have emerged as an alternative to traditional chemical catalysis due to their high specificity, non-toxic nature, and mild conditions.[2] Laccase (EC 1.10.3.2), a highly attractive biocatalyst in modern organic synthesis, is a multi-copper glycoprotein belonging to the family of oxidoreductases.[3] It is well known to catalyze the aerobic one-electron oxidation of phenolic compounds,[4] benzylamides,[5] and hydroxylamines[6] in the presence of O_2 as an electron acceptor, and to produce H_2O exclusively as a by-product.

The range of laccase substrates can be extended by the simultaneous use of the enzyme and redox mediators such as 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) and *N*-hydroxybenzotriazole (HBT). In the presence of laccase mediators, the enzyme efficiently offers oxidation of non-phenolic substrates, including various alcohols,[7] ethers,[8] and aromatic methyl groups.[9] Recently, the transformation of C–N bonds to C=N bonds during the oxidation of 1,4-dihydropyridines to pyridines was performed by laccase/ABTS under mild reaction conditions.[10]

Quinazolinones are an important family of nitrogen-containing heterocycles that play a significant role in the pharmaceutical community for their diverse range of biological and pharmacological properties, such as anticancer,[11] antimalarial,[12] antidiabetic,[13] anticonvulsant,[14] and hypolipidemic[15] activities. They are useful building blocks for many natural products like luotonin A,[16] glycosminine,[17] rutaecarpine,[18] and pharmaceutical agents like methaqualone, which has sedative-hypnotic and antimalarial properties.[19] Additionally, quinazolinones inhibit tubulin polymerization[20] and the epidermal growth factor receptors of tyrosine kinase.[21] In view of their various biological activities, numerous methods have been developed for the synthesis of quinazolinone derivatives.[22] The most common approach is through a three-component reaction of isatoic anhydride,



Scheme 1. One-pot synthesis of quinazolinones starting directly from benzyl alcohols, isatoic anhydride, and amines.

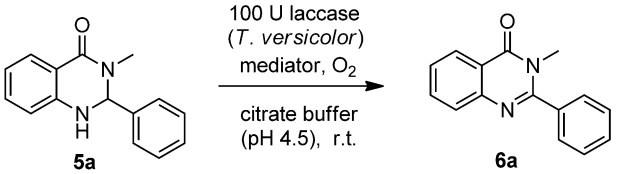
amines, and aldehydes, followed by the oxidation of the aminal intermediate. Oxidation with toxic and non-renewable oxidants, such as 2,3-dichloro-5,6-dicyano-l,4-benzoquinone (DDQ),[23] I_2,[24] MnO_2,[25] $NaHSO_3$,[26] and $KMnO_4$[27] is one of the drawbacks of these systems. However, since aldehydes are more volatile, toxic, and unstable than their corresponding alcohols, the one-pot oxidative synthesis of quinazolinones directly from alcohols with chemical catalysts has been recently investigated. Under hydrogen transfer conditions, the condensation of primary alcohols with aminobenzamides using complexes of iridium[28] and ruthenium[29] has been explored. Gei and coworkers reported the iodine-catalyzed synthesis of quinazolinones from alcohols using dimethyl sulfoxide (DMSO) as an oxidant in dimethyl carbonate.[30] A very recent report described the oxidative synthesis of nitrogen-containing heterocycles, such as quinazoline and quinazolinone employing $FeCl_3$[31] as catalyst. The reaction was carried out using *tert*-butyl hydroperoxide (TBHP) as an oxidant and DMSO as an organic solvent. Although some methods for the synthesis of quinazolinones have been developed, it is highly desirable to investigate more convenient and environmentally friendly approaches.

In the present study, the enzymatic oxidation of 2,3-dihydroquinazolin-4(1*H*)-ones using laccase was investigated. Moreover, a one-pot reaction for the synthesis of quinazolinones *via* a tandem sequence starting from alcohols **1**, isatoic anhydride **3**, and amines **4** using the laccase-mediator system in a citrate buffer is described (Scheme 1).

Results and Discussion

In order to develop an environmentally friendly catalytic system for the synthesis of biologically important heterocyclic compounds using enzymes, the oxidation of 2,3-dihydroquinazolin-4(1*H*)-one **5a** using laccase as the model reaction was investigated. Initially, the reaction was carried out in the presence of laccase from *Trametes versicolor* at room temperature under

Table 1. Oxidation of 2,3-dihydroquinazolin-4(1*H*)-one **5a**, in the presence of different mediators, by laccase.



Entry	Mediator (mol%)	Time [h]	Yield [%][a]
1	–	24	–
2	HBT (5 mol%)	6	58
3	HBT (10 mol%)	6	76
4	HBT (20 mol%)	6	85
5	ABTS (10 mol%)	6	72
6	TEMPO (10 mol%)	6	53
7	NHS (10 mol%)	10	12
8	DMP (10 mol%)	10	18
9	gallic acid (10 mol%)	10	15
10	4-hydroxycinnamic acid (10 mol%)	10	21

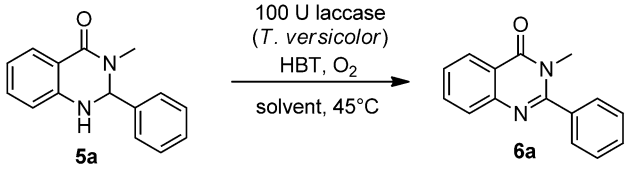
[a] Isolated yield.

O_2 in a citrate buffer (pH 4.5). No reaction took place, even after stirring the reaction mixture for 24 h (Table 1, entry 1). The addition of H_2O_2 as an oxidant gave only a trace of the product (10%, data not shown), therefore various mediators were evaluated for this reaction. The desired product was obtained in low yields in the presence of *N*-hydroxysuccinimide (NHS), 2,6-dimethoxyphenol (DMP), gallic acid, and 4-hydroxycinnamic acid (Table 1, entries 7–10), and 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) also provided moderate yields (Table 1, entry 6). Among the mediators screened, the highest yield was observed using HBT (Table 1, entry 4); however, the reaction was also performed using ABTS to produce a good yield (Table 1, entry 5).

Subsequently, the effect of the amount of the mediator on the reaction was explored. Decrease in the amount of the HBT from 10 mol% to 5 mol%, led to a decrease in the yield (Table 1, entry 2 *vs.* entry 3). Furthermore, when the amount of HBT was increased from 10 mol% to 20 mol%, the yield improved from 76 to 85%, respectively (Table 1, entry 4 *vs.* entry 3) However, more than 20 mol% of HBT did not increase the yield anymore. It should be noted that for each mediator, a blank reaction was considered without the enzyme, and in the absence of laccase, no product was detected.

The effect of temperature on the reaction yield was also studied, and it was found that increasing the reaction temperature up to 45 °C improved the yield of the product up to 90%, but further increases in temperature resulted in a decrease in the yield due to enzyme deactivation[32] (see the Supporting Information, Figure S1).

Table 2. Solvent optimization for the oxidation of 2,3-dihydroquinazolin-4(1*H*)-one **5a** by laccase.



Entry	Solvent	Time [h]	Yield [%][a]
1	water	6	72
2	citrate buffer 1 M, pH 4.5	6	90
3	THF	24	–
4	DMF	24	–
5	MeCN	24	–
6	[Bmim]PF_6	6	65
7	citrate buffer 1 M, pH 4.5/THF (5:1; v/v)	24	25
8	citrate buffer 1 M, pH 4.5/DMF (5:1; v/v)	24	44
9	citrate buffer 1 M, pH 4.5/MeCN (5:1; v/v)	24	21
10	citrate buffer 1 M, pH 4.5/[Bmim]PF_6 (5:1; v/v)	6	81

[a] Isolated yield.

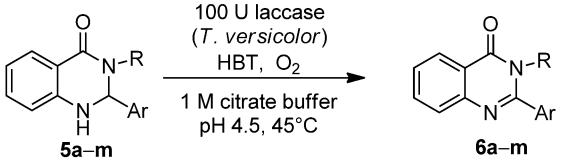
In order to determine the best solvent for the reaction, the laccase-catalyzed oxidation of **5a** was studied in aqueous media and diverse organic solvents and, as can be seen in Table 2, citrate buffer (pH 4.5, 0.1 M) was the best medium (Table 2, entry 2). No reaction took place in pure organic solvents, such as THF, DMF, and MeCN, due to deactivation of the enzyme (Table 2, entries 3–5). Interestingly, product **6a** was formed in a yield of 65% in 1-butyl-3-methylimidazolium hexafluorophosphate ([Bmim]PF_6), a prevalent ionic liquid (IL), as the green organic medium (Table 2, entry 6). In the mixture of citrate buffer and organic solvents, the laccase-catalyzed oxidation was carried out with moderate yields, in the range of 21% to 44% (Table 2, entries 7–9). Therefore, citrate buffer was the best medium.

Employing the optimized conditions, the oxidation of a number of 2,3-dihydroquinazolin-4(1*H*)-one derivatives **5a–m** to quinazolinones **6a–m** was investigated and the results are summarized in Table 3.

Due to the importance of multi-component reactions,[33] and the ability of laccase to catalyze the oxidation of benzyl alcohols to benzylaldehydes,[7] A one-pot synthesis of quinazolinones **6a** from benzyl alcohol, isatoic anhydride, and methylamine in the presence of laccase/HBT at 45 °C in a citrate buffer (pH 4.5) was developed. The ^{1}H NMR spectra of the crude reaction mixture show that compounds **5a** (74%) and **6a** (11%) were the only isolable products obtained by quenching the reaction after 20 h at 45 °C. Increasing the temperature of the reaction (70 °C) decreased the yields of the products without significant changes in the ratio of the isolable products (**5a** and **6a**), which could be attributed to the enzyme deactivation in high temperatures.

In order to enhance the formation of **6a**, the amount and method of enzyme addition was screened. After some experimentation, it was determined that the optimal yield of quinazolinone (**6a**) (85%) could be achieved when laccase was added at various time intervals during the reaction. It is also worth mentioning that compound **5a** could be obtained from benzaldehyde, isatoic anhydride, and methylamine at 45 °C in a citrate buffer (pH 4.5) at a high yield (84%). This result was improved in the presence of laccase by up to 98%. Moreover, various

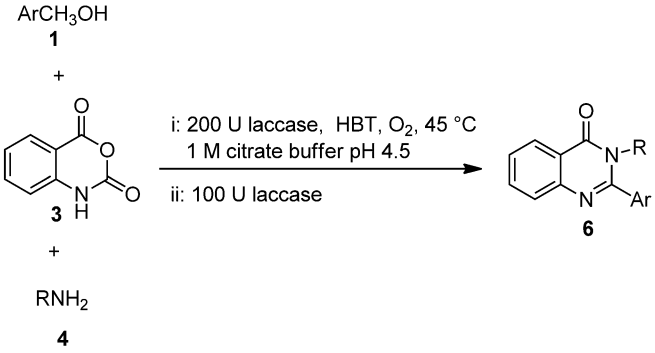
Table 3. Oxidation of dihydroquinazolinones to quinazolinones using laccase and O_2 as the oxidant.



Entry	**5**	Ar	R	Time [h]	Yield [%][a]
1	**a**	H	CH_3	6	90
2	**b**	4-Cl	CH_3	6	92
3	**c**	4-OMe	CH_3	6	90
4	**d**	H	CH_2CH_3	6	92
5	**e**	4-Cl	CH_2CH_3	6	90
6	**f**	4-Me	CH_2CH_3	6	88
7	**g**	4-OMe	CH_2CH_3	6	86
8	**h**	3-NO_2	CH_2CH_3	6	87
9	**i**	H	H	6	88
10	**j**	4-Me	H	6	85
11	**k**	4-OMe	H	6	81
12	**l**	H	$C_6H_5CH_2$	10	76
13	**m**	4-Cl	$C_6H_5CH_2$	10	74

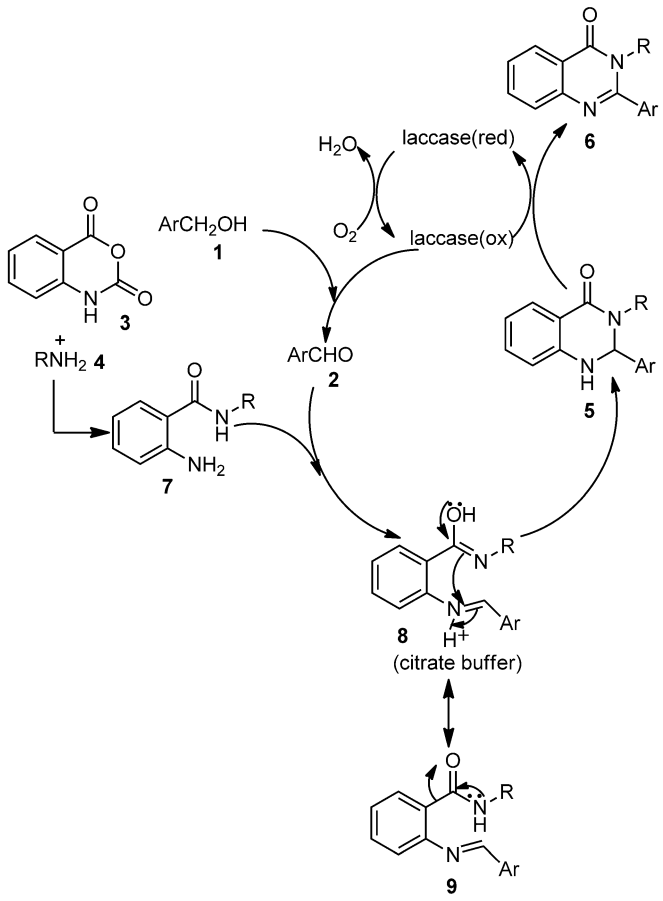
[a] Isolated yield.

Table 4. One-pot synthesis of quinazolinones **6a–m** from benzyl alcohol catalyzed by laccase.



Entry	6	Ar	R	Time [h]	Yield [%][a]
1	**a**	H	CH_3	20	85
2	**b**	4-Cl	CH_3	20	73
3	**c**	4-OMe	CH_3	20	87
4	**d**	H	CH_2CH_3	20	74
5	**e**	4-Cl	CH_2CH_3	20	68
6	**f**	4-Me	CH_2CH_3	20	81
7	**g**	4-OMe	CH_2CH_3	20	87
8	**h**	3-NO_2	CH_2CH_3	20	62
9	**i**	H	H	20	78
10	**j**	4-OMe	H	20	87
11	**k**	4-Me	H	20	85
12	**l**	H	$C_6H_5CH_2$	30	73
13	**m**	4-Cl	$C_6H_5CH_2$	30	67

[a] Isolated yield.



Scheme 2. Plausible mechanism for laccase/HBT catalyzed aerobic oxidative synthesis of quinazolinones.

benzyl alcohols were examined and found to react with isatoic anhydride and some amines, and the results are summarized in Table 4. The yield of the product seems to be affected by the nature of the substituent on benzyl alcohol. This reflected the lower reactivity of benzyl alcohols with electron-withdrawing groups toward oxidation to aldehydes.

A plausible mechanism for this reaction is proposed in Scheme 2. First, the reaction involves the dehydrogenation of primary alcohol **1** to aldehyde **2** using laccase/HBT, followed by the reduction of one molecule of oxygen to two molecules of water. Then, isatoic anhydride **3** reacts with amine **4** to afford aminobenzamide **7**. Subsequently, the condensation of **7** with aldehyde **2** affords 2,3-dihydroquinazolin-4(1*H*)-one **5** in a citrate buffer. Finally, the second laccase-mediated oxidation is the dehydrogenation of **5** to give the quinazolinone product **6**.

Conclusions

In summary, an efficient and environmentally friendly approach for the oxidation of 2,3- dihydroquinazolin-4(1*H*)-ones in the presence of laccase as a catalyst and HBT was demonstrated. In addition, the synthesis of quinazolinones *via* a tandem reaction starting directly from alcohols using the laccase-mediator system in a citrate buffer was also developed. This green procedure represents several attractive characteristics, such as the use of O_2 as a non-toxic oxidant and the production of water as the only by-product in the process. Additionally, the reactions were conducted in a citrate buffer, representing a green reaction medium under mild conditions.

Experimental Section

General Experimental Details

Laccase from *Trametes versicolor* ($\geq$20 mg) was purchased from Sigma–Aldrich (St. Louis, MO, USA). All chemicals and solvents were obtained commercially and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-300 Avance spectrometer at 300.13 and 75.47 MHz, respectively. The chemical shifts are given in δ relative to TMS, and the coupling constant (J) values are given in Hz. The splitting patterns are designated as s (singlet), d (dou-

blet), t (triplet), and m (multiplet). Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

General Procedure for the Oxidation of 2,3-Dihydroquinazolin-4(1*H*)-ones 5a–m to Quinazolinones (6a–m)

To a magnetically stirred solution of 2,3-dihydroquinazolin-4(1*H*)-one **5** (1.0 mmol) in a citrate buffer (0.1 M, pH 4.5, 10 mL) under O_2, were added HBT (30 mg, 0.2 mmol) and laccase from *T. versicolor* (100 U, 20 mg), and the reaction mixture was stirred at 45 °C for the time given in Table 4. Then, the reaction mixture was extracted with ethyl acetate (3×15 mL), and the organic layer was dried over anhydrous Na_2SO_4. The crude product was purified by silica gel column chromatography using hexane/ethyl acetate (75:25) as a mobile phase.

General Procedure for the One-Pot Synthesis of Quinazolinones (6a–m)

To a magnetically stirred solution of benzyl alcohol **1** (1.0 mmol) in a citrate buffer (0.1 M, pH 4.5, 10 mL) under O_2, were added HBT (30 mg, 0.2 mmol) and laccase from *T. versicolor* (200 U, 40 mg), and the reaction mixture was stirred at 45 °C. Then, isatoic anhydride **2** (1 mmol), amine **3** (1 mmol) were added, and the mixture was stirred until the substrates were fully consumed, which was indicated by TLC. Next, 100 U laccase under O_2 were added, and the reaction mixture was extracted with ethyl acetate (3×15 mL). The organic layer was dried over anhydrous Na_2SO_4, and the crude product was purified by silica gel column chromatography using hexane/ethyl acetate (75:25) as a mobile phase.

Analytical data for 2-phenylquinazolin-4(3*H*)-one (6a): white solid; mp 133–135 °C; (lit.,[34] 128–129 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.34 (d, J = 7.7 Hz, 1H), 7.75–7.78 (m, 2H), 7.49–7.57 (m, 6H), 3.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.74, 156.16, 147.34, 135.41, 134.35, 130.1, 128.93, 128.01, 127.53, 126.03, 126.7, 120.5, 34.3; anal. calcd. (%) for $C_{15}H_{12}N_2O$: C 76.25, H 5.12, N 11.86; found: C 76.17, H 4.97, N 11.94.

Acknowledgements

This work was supported financially by the Biotechnology Research Center, Tehran University of Medical Sciences, Tehran, Iran to M.A.F. (grant No. 92-02-90-23628).

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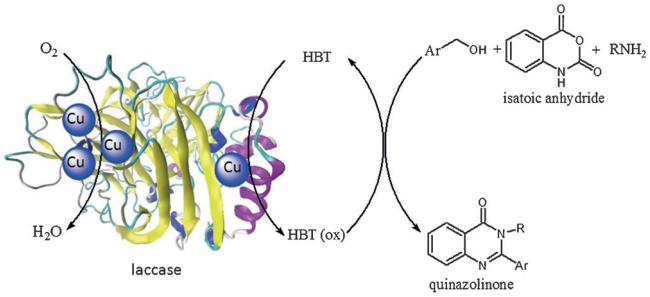

HBT: *N*-hydroxybenzotriazole

