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T. Rosenau [a] , A. Potthast [b] , C. L. Chen [c] & J. S. Gratzl [c]

[a] Institut für Organische Chemie, Technische Universität Dresden , Mommsenstr. 13, Dresden, D-01062, Germany

[b] Institut für Holzund Pflanzenchemie, Technische Universität Dresden , PiennerStr. 23, Tharandt, D-01737, Germany

[c] Department of Wood and Paper Science , North Carolina State University , Raleigh, NC, 27695-8005, USA

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A MILD, SIMPLE AND GENERAL PROCEDURE FOR THE OXIDATION OF BENZYL ALCOHOLS TO BENZALDEHYDES

T. Rosenau[a], A. Potthast[b], C.L. Chen[c,*], and J.S.Gratzl[c]

[a] Institut für Organische Chemie, Technische Universität Dresden, Mommsenstr. 13, Dresden, D - 01062, Germany
[b] Institut für Holz- und Pflanzenchemie, Technische Universität Dresden, Pienner Str. 23, Tharandt, D - 01737, Germany
[c] Department of Wood and Paper Science, North Carolina State University, Raleigh, NC, 27695-8005, USA

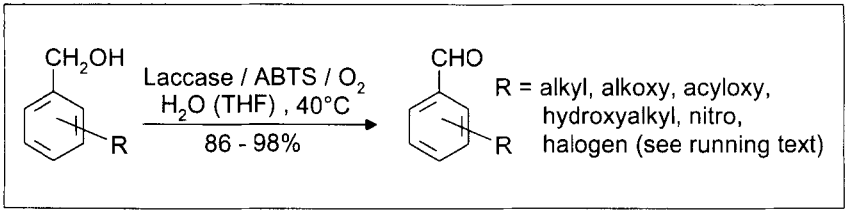
ABSTRACT: The enzyme/cofactor system laccase/2,2'-azino-bis(3-ethyl-benzothiazoline-6-sulfonic acid) catalyzes the oxidation of benzyl alcohols to the corresponding benzaldehydes by molecular oxygen. The reaction proceeds under physiological conditions to yield the products quantitatively.

Substituted benzaldehydes are very commonly used synthons in organic syntheses. Like methods for the direct introduction of the CHO group into aromatic systems,[1] oxidation of benzyl alcohols belongs to the set of standard methods.[2] Unfortunately, almost all of the procedures known so far have major disadvantages. There is always the risk of further oxidizing the benzaldehyde formed, since this aldehyde is more readily amenable to oxidation than the benzyl alcohol. Moreover, procedures that require drastic reaction conditions often imply the absence of other substituents on the aromatic ring. Other methods give quite

* To whom correspondence should be addressed.

good yields, but apply rather toxic reagents or require sophisticated preparative techniques.[3]

In this paper, we present a new approach to the oxidation of substituted benzyl alcohols to the corresponding benzaldehydes by molecular oxygen using the laccase / 2,2'-azino-bis(3-ethyl-benzothiazoline-6-sulfonic acid) [ABTS] catalyst system[4] as shown in the following scheme.



There are substantial advantages in this reaction which make it superior to almost all known procedures for the oxidation of benzyl alcohols to benzaldehydes. The reaction proceeds quantitatively, since the benzyl alcohols, acting as substrates, and the oxygen, acting as oxidant, are bound to the enzyme during the reaction. The oxidation stops selectively at the aldehyde stage, further oxidation to the acid was not observed. The yield, usually ranging from 85 to 98% after work-up, seems to be independent of the type of substituents and the substitution pattern on the aromatic ring, as investigated so far.

The only substituents interfering with the catalytic reaction are phenolic OH groups, aromatic and benzylic NH_2 groups, and activated aromatic methyl groups. Phenols are protected by etherification or esterification.[5] Aromatic or benzylic NH_2 groups must be protected by reactions with appropriate carbonyl compounds forming *Schiffs* bases.[5] The effect of the laccase/ABTS couple on aromatic methyl groups is currently being investigated in our group. However, an effective means of protection for activated methyl groups on aromatic rings has not yet been found. It should be mentioned that the catalyst system laccase/ABTS does not influence aliphatic OH or NH_2 groups, and therefore, these may remain

unprotected during the reaction. Double bonds, ether and ester bonds, and other frequently occurring substituents on aromatic rings, such as halogens or nitro groups, are also unaffected.

The use of gaseous oxygen as the oxidant, and the catalytic amounts of auxiliaries applied make the procedure extremly "clean" and environmentally friendly. This is also reflected by the use of water as the solvent. However, in the case of water insoluble benzyl alcohols, THF or dioxane must be added to the reaction mixture until all of the starting material is dissolved. Addition of these organic solvents does not impair the enzymatic activity of the catalyst or lower the yields. Since both the enzyme and the co-substrate remain in the aqueous phase after completion of the reaction and extraction of the product with CH_2Cl_2, benzaldehydes of very high purity are obtained, making further purification unnecessary.

Instead of benzyl alcohols, the corresponding benzyl halogenides can be used. These benzyl halogenides are hydrolyzed to benzyl alcohols under the

Table. Substituents on the aromatic ring of the benzyl alcohol, that do not interfere with the enzymatically catalyzed oxidation to benzaldehydes presented.

Substituent	Example for benzyl alcohol	Product obtained, overall yield
alkyl[a]	p-ethylbenzylalcohol	p-ethylbenzaldehyde, 92%
alkoxy[b]	p-methoxybenzylalcohol	p-methoxybenzaldehyde, 90%
alkylcarbonyl-oxy, aroyloxy[c]	p-acetoxybenzylalcohol 3-methoxy-4-benzoyloxy-benzylalcohol	p-acetoxybenzaldehyde, 92% 3-methoxy-4-benzoyloxybenz-aldehyde,92%
nitro	p-nitrobenzylalcohol	p-nitrobenzaldehyde, 98%
halogen[d]	m-chlorobenzylalcohol	m-chlorobenzaldehyde, 92%

[a] Except aromatic methyl groups, see running text.

[b] Useful for oxidation of α-hydroxymethylphenols after protection of the OH group by etherification.

[c] Useful for oxidation of α-hydroxymethylphenols after protection of the OH group by esterification.

[d] Iodine as substituent was not tested.

prevailing conditions. In addition, the catalyst seems to have a beneficial effect on the hydrolysis rate. Benzylamines show the same reaction behavior, and can therefore act as substitutes for the benzyl alcohols. All of these advantages compensate for the drawback of prolonged reaction times (24h to 48h) that are required to achieve complete conversion of the starting material.

In the preceding table, the different substituents that do not interfere with the enzyme-catalyzed reaction are given, including one representative example for each class of substituents. Numerous benzyl alcohols were oxidized to the corresponding benzaldehydes according to the method presented. The yields were generally high, above 90%. No by-products or deviations from the desired course of reaction were observed. The general procedure given in the experimental part is applicable to all benzyl alcohols meeting the given requirements for substituents on the aromatic ring.

In summary, a new method for oxidizing benzylalcohols to benzaldehydes is added to the chemist's list of standard synthetic methods. The mild reaction conditions, and the high specificity due to the enzyme catalyst promise broad applicability of the reaction in organic synthesis.

EXPERIMENTAL

2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) was purchased as diammonium salt from Aldrich Chemical Co. All benzyl alcohols used as starting material were of reagent grade from commercial sources or synthesized according to known procedures. Deionized water was used, other solvents were of HPLC grade. Laccase from *Coriolus versicolor* was purchased from Merican Corp., Tokyo. The activity was determined by the p-hydroxy-mandelic acid assay.[6] The composition of the reaction mixtures and the purity of the products were determined by GC (Hewlett Packard Model 5890 Series II, capillary column DB-5, 30 m x 0.32 mm i.d.) and GCMS (Hewlett- Packard Model 5985B, EI, 70 eV). Low attenuation was used to ensure that no by-products in small amounts remained undetected.

Laccase/ABTS-catalyzed oxidation of substituted benzyl alcohols to benzaldehydes - general experimental procedure.

A solution of a substituted benzyl alcohol (10-20 mmol), and ABTS-$(NH_4)_2$ (0.1644 g; 0.3 mmol) in 50 mL of acetate buffer pH 4.5 was placed in a 250 mL flask equipped with a magnetic stirrer and warmed to 40°C in a water bath. In case of water insoluble benzyl alcohols, the substrate was dissolved in 30 mL THF and added to the aqueous buffer solution. 0.1 mL laccase (laccase activity, 1.1 x 10^4 / mL) was added, the reaction vessel was flushed with O_2 for 1 min and closed. Upon addition of the enzyme, the colorless solution turned into deep blue-green immediately. The temperature was maintained at 40°C during the reaction. After 24 h, a 0.5 mL sample of the reaction mixture was taken, extracted with CH_2Cl_2 and the resulting organic solution was analyzed by GCMS. If starting material was still present, an additional 0.03 mL of the above enzyme and 0.05 g of the co-substrate ABTS was added. The reaction mixture was flushed with O_2 for 5 min and kept at 40°C for additional 24 h. After cooling to the room temp, the reaction mixture was extracted three times with CH_2Cl_2. The aqueous layer was discarded. The organic phase was dried over $MgSO_4$ and the solvent slowly removed under reduced pressure. The corresponding benzaldehyde obtained did not require further purification.

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