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Synthesis of aromatic aldehydes by laccase-mediator assisted oxidation

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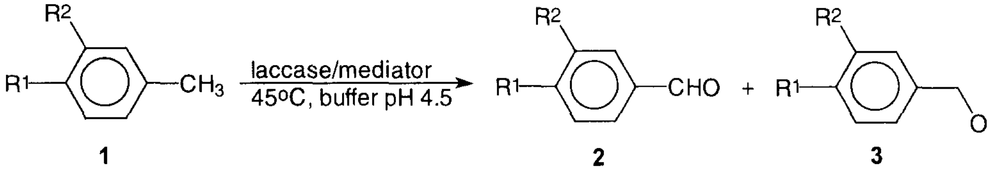
Abstract

Aromatic aldehydes can be prepared in aqueous medium by oxidation of the corresponding methyl aromatic compounds in the presence of oxygen, the enzyme laccase and catalytic amounts of various N-hydroxy compounds. Allylic alcohols also gave the corresponding aldehydes in good yield. Competing reactions reveal that the N-hydroxy compound is involved in the rate determining step of the reaction.

The selective oxidation of aromatic hydrocarbons into aldehydes is still a challenging task because of unsatisfying selectivity and the formation of carboxylic acids [1]. Synthetic methods using enzymes promise selective transformations under mild conditions in aqueous medium. Laccase [2] from *Trametes versicolor* in combination with a so-called "mediator", for example ABTS [3] or 1-hydroxy-1H-benzotriazole (HOBT) is known as bleaching reagent for pulps [4-7].



(1)

We were able to oxidize various methyl benzenes **1** to the corresponding aldehydes **2** by laccase and 0.11 equiv. HOBT in the presence of air; the benzyl alcohols **3** are formed as intermediates (eq. 1, table 1). Carboxylic acids are formed only in traces (<1 %). In accordance to ref.[7] we found very low conversions with ABTS as mediator which is in contrast to ref. [8]. Substituted derivatives of N-hydroxyphthalimide (HPI), for example the 3-amino or the 3- and 4-methyl derivative, give high yields of the aldehyde **2**, whereas HPI itself or derivatives with electron-attracting groups, e.g. 4-NO_2, are ineffective mediators (table 1). This implies that electronic effects play an important role for the mediator activity in the HPI-series. Electron rich methyl benzenes are favorably oxidized. Preliminary results show that in xylenes only one methyl group is oxidized. 4-Aminobenzaldehyde which undergoes rapid polymerization can be easily obtained in solution from the laccase mediator oxidation of 4-methylaniline. Methyl benzenes bearing electron withdrawing groups like the 4-cyano group give only low conversions.

Allylic alcohols 3-methyl-2-buten-1-ol (**6**, $R^1 = R^2 = CH_3$) and cinnamic alcohol (**6**, R^1 =H, R^2 = phenyl) can be oxidized analogously to the corresponding aldehydes (eq.2) whereas oxidation of the methyl groups was not observed. Propenyl benzene and the 4-methoxy and 3,4-dimethoxy

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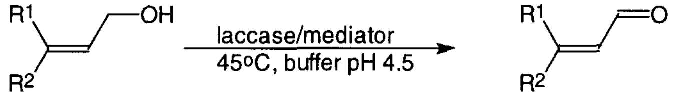
Table 1

Oxidation of methyl benzenes **1** with laccase and mediators in the presence of air.[a]

R^2, R^1 in **1**	mediator (equiv.)	laccase (IU)[b]	% **2**	% **3**	% **1**
3-OCH_3, 4-OCH_3	HOBT (0.11)	113	20	3	63[c]
3-OCH_3, 4-OCH_3	HOBT (0.23)	226	49	4	25[c]
3-OCH_3, 4-OCH_3	HOBT (0.45)	452	76	4	23[c]
3-OCH_3, 4-OCH_3	HOBT (1.1)	1130	99	0	3[c]
3-OCH_3, 4-OCH_3	HPI (0.11)	113	9	4[d]	
3-OCH_3, 4-OCH_3	3-amino-HPI (0.23)	226	44	37	12[d]
3-OCH_3, 4-OCH_3	3-amino-HPI (0.45)	452	93	5	
3-OCH_3, 4-OCH_3	4-methyl-HPI (0.23)	226	47	18	35[c]
3-OCH_3, 4-OCH_3	4-methyl-HPI (0.45)	452	50	12	2[c]
3-OCH_3, 4-OCH_3	3,4-dimethoxy-HPI (0.11)	113	26	7[d]	
3-OCH_3, 4-OCH_3	3,5-dimethyl-HPI (0.11)	113	33	7[d]	
3-OCH_3, 4-OCH_3	4-nitro-HPI (0.11)	113	0.2	1.3[d]	
3-OCH_3, 4-OCH_3	N,N'-dihydroxypyromellitic-diimide (0.11)	113	0.1	2.7[d]	
4-OCH_3	HOBT (0.11)	113	48	28[d]	
4-OCH_3	3-amino-HPI (0.11)	113	61	7[d]	
4-CN	3-amino-HPI (0.11)	113	1-10	<1[d]	

[a] procedure: 1.59, 0.795 or 0.398 mmol of **1** in 1 ml ethanol are diluted with 22 ml of a 100mM citric acid/phosphate buffer pH 4.5. 0.18 mmol of a mediator are added at 45°C and after 10 min. 10 mg laccase (18 IU/mg [4]) in 10 ml water. The mixture is stirred (22 h) under a slight stream of air. GC analysis is performed after adding 22 ml ethanol; [b] per mmol substrate, laccase is available by our biochemistry department, activity measurement in [4]; [c] absolute yield by GC standard analysis; [d] relative yield based on unconverted substrate.



(2)

6 5

derivative were completely oxidized at the double bond to give a mixture of 1-phenyl-1,2-propanediols, 1-phenyl-2-hydroxy-1-propanones and benzaldehydes.

In the laccase mediator oxidation N-O-radicals are involved [6, 9]. In competing experiments with mixtures of 3,5- and 2,3-dimethoxybenzyl alcohol as substrate and laccase-air-HOBT and laccase-air-4-methyl-HPI as oxidizing reagent we obtained competition constants κ [10] of 3.8 and 4.9, respectively. When lead dioxide was used as oxidant instead of laccase the same values of κ were obtained within experimental error. This proves that laccase is not involved in the rate determining step but the mediator is. We therefore assume that the substituted NO-radicals created by laccase react with the substrate under hydrogen abstraction thus closing the redox cycle. A further process leads to deoxygenation of the mediator [6].

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