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MUSHROOM TYROSINASE CATALYSED COUPLING OF HINDERED PHENOLS : A NOVEL APPROACH FOR THE SYNTHESIS OF DIPHENOQUINONES AND BISPHENOLS

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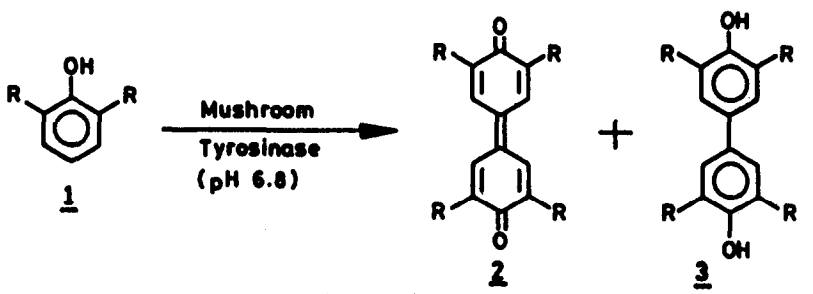
Abstract: An efficient oxidative carbon-carbon coupling of hindered phenols leading to diphenoquinones and bisphenols by mushroom tyrosinase is reported.

Phenol coupling is an important synthetic tool and an essential step in the biosynthesis of many alkaloids and other natural products[1]. The reagents most extensively employed to effect oxidative coupling (e.g. Ferricyanide, $FeCl_3$, MnO_2, PbO_2, Ag_2O, etc) often suffer from poor selectivity and usually give a mixture of quinones, dimers and polymers[2].

Mushroom tyrosinase is known to oxidise phenols and catechols to ortho quinones efficiently in the presence of molecular oxygen[3]. However, to the best of our knowledge, no systematic attempt is made to study the oxidation of 2,6-disubstituted phenols (ortho positions blocked) by tyrosinase enzyme. Due to the considerable importance of phenolic oxidation reactions[4], and in persuance of our ongoing study[5,6] we envisioned that 2,6-disubstituted phenols might undergo C-C coupling reaction upon tyrosinase catalysed oxidation. We disclose our preliminary observations of oxidation of hindered phenols by mushroom tyrosinase with plausible mechanistic rationale.



1 2 3

SCHEME-I

It is interesting to note that diphenoquinones (2) were exclusive products when the reaction was performed in only phosphate buffer (pH 6.8). However, when acetonitrile (in which the solubility of phenols were limited) was used as co-solvent bisphenols (3) were also isolated, though in poor yields than 2 (Table 1).

Another important observation was noted that efficiency of the enzymatic oxidation depends upon the nature of substitution of phenols. A kinetic analysis of this reaction (Fig.1) revealed that phenols bearing electron donating substituents oxidise efficiently. In fact, 2,6-dichlorophenol

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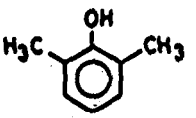
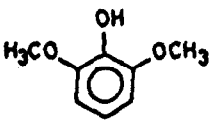
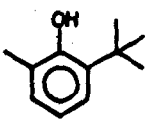
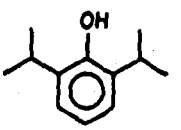
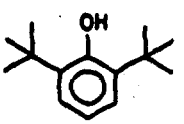
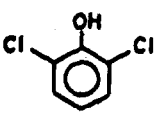
did not undergo oxidation at all (Table 1). Since it is obvious that diphenoquinones (2) and biphenols (3) would be arising from the dimerisation of aryloxyradical intermediate, a probable mechanistic route could be envisaged by considering a single electron transfer from phenols to tyrosinase followed by proton loss.

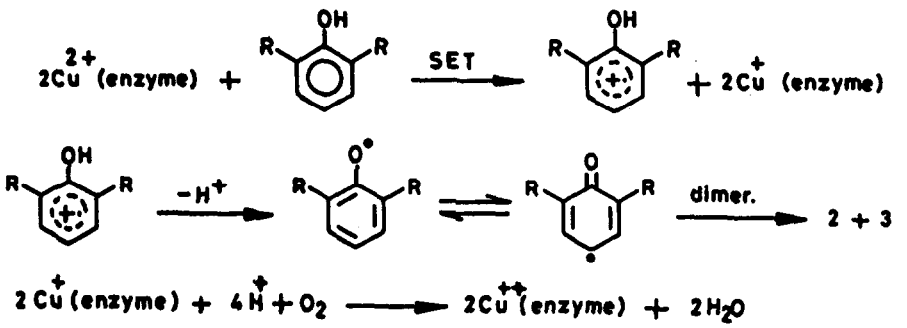
Table 1: Mushroom Tyrosinase Catalysed Oxidation of hindered phenols.

Entry	Substrate	Reaction time (in hrs)	Product yield (%)	
			2a – 2f	3a – 3f
1a		9	96 70[a]	— 20[a]
1b		9	98 72[a]	— 20[a]
1c		55	— 50[a]	— 24[a]
1d		58	— 46[a]	— 24[a]
1e		60	— 40[a]	— 20[a]
1f		—	—	—

a - yields obtained when acetonitrile was used as cosolvent.
b - satisfactory spectral data was obtained for all compounds.

This argument is supported from our observation of dependence of oxidation rate upon the substitution pattern of the phenol. Since tyrosinase enzymes are termed "copper enzymes" as they contain copper presumably in cupric form[7], therefore, a plausible mechanism based

upon the above observation could be as depicted in Scheme II.



SCHEME-II

The failure of oxidation to occur under an argon atmosphere also supports the above mechanism.

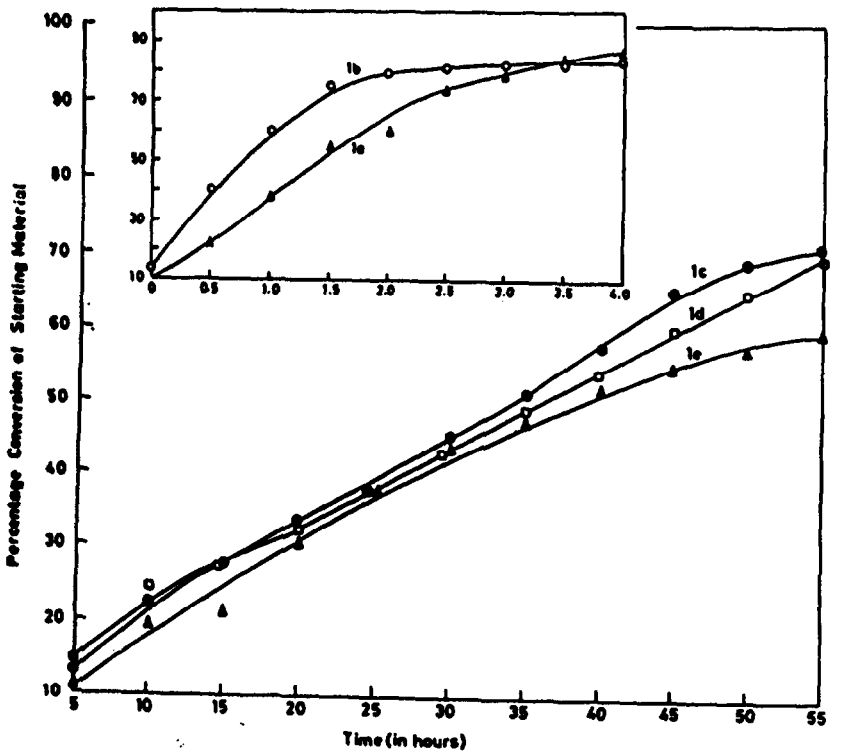


Figure 1 - Kinetics of the mushroom tyrosinase catalysed oxidation of hindered phenols(1a-f)

It is noticed that dissolved oxygen was sufficient for the oxidation, however, oxidation rate was found to be considerably enhanced when slow stream of oxygen was bubbled through the reaction mixture. Some copper amine complexes are also implicated to participate in phenol oxidation where reduction of Cu^{++} to Cu^{+} is very well established[8] which also substantiates our mechanism.

A typical reaction procedure:

To a stirred solution of 2,6-disubstituted phenols (0.01 M) in 50 ml of phosphate buffer (0.05 M; pH 6.8) was added 0.5 mg (50,000 units) tyrosinase enzyme. As the reaction proceeded the change in colour from colourless to reddish brown was noticed and in most of the cases diphenoquinone was precipitated out. However, in cases where acetonitrile was used as co-solvent the reaction mixture was extracted with ethylacetate and purified by normal chromatography.

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