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Regioselective Enzymatic Epoxidation of (E)-(E)-Piperylpiperidine

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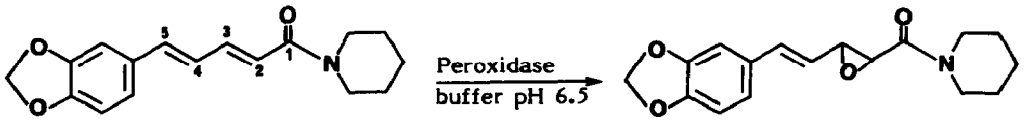
Abstract : Peroxidase catalyzed regioselective epoxidation of (E)-(E)-Piperylpiperidine is described.

The discovery and development of enzymatic processes to effect asymmetric transformations as a means to prepare optically active intermediates of enantiomeric specificity in relation to natural products is currently popular area of research in organic chemistry. Epoxides are very useful and extensively employed intermediates for the synthesis of biologically important compounds[1] and their availability in optically pure form, greatly increase their usefulness as synthons. Microbial epoxidations can provide an easy access to simple epoxides of high optical purity but it has its limitations for preparative scope[2]. Enzymes as biocatalysts in regio and stereoselective synthesis of organic molecules are now well recognized[3]. The use of peroxidase as a catalyst in the synthesis of organic molecules are known, however selective epoxidations are not well studied[4]. As a part of our current interest in the application of enzymes as biocatalysts[5], we describe a new method for the regioselective epoxidation of (E)-(E)-piperylpiperidine (1) to 4,5-(trans)-2,3-epoxy piperylpiperidine (2), using Horseradish peroxidase.



The alkaloid (E)-(E)-piperylpiperidine (1) is the principal constituent of berries of piper nigrum (black pepper) which is commonly used as spices and as Indian indigenous medicine[6]. The compound was isolated from seeds of piper nigrum following literature methods[7].

Compound 1 (100 mg) was dissolved in 0.1 M sodium phosphate buffer pH 6.5 (20 ml) and to this mixture peroxidase 1200 units (Type VI A from Horseradish obtained from Sigma Chemical Co USA), 0.5 ml 1% H_2O_2 were added and incubated for 18 hours at 37°C. After the incubation the mixture was extracted with chloroform, dried over magnesium sulphate and evaporated under reduced pressure to give the crude epoxide, which was purified by column chromatography (silica gel:chloroform-methanol, 98:2, yield 75%). The structure of the com-

pound **2** was confirmed by spectral data[8].

The results of the study show that the high substrate regiospecific epoxidation was observed at 2,3 double bond due to particular topology of the enzyme active site.

In conclusion, the present investigation using Horseradish peroxidase provides a mild and regioselective procedure for the preparation of 4,5-(trans)-2,3 epoxy piperylpiperidine. Further studies on mechanism of the epoxide reaction and synthetic applications of the compound are currently in progress.

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8. Physical and spectral data for **2**: m.p. 186-187°C, Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.35; N, 4.65. Found: C, 67.60; H, 6.34; N, 4.49, $[\alpha]_D^{25}$ +5.99 (c 0.5, EtOH). IR (KBr): 1650 (C=O), 1620 (C=C), 1500, 1475, 1238, 1000 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.55-6.72 (3H, m, Ar-H), 5.91 (1H, d, J=1.45 Hz, methylene dioxy-H), 5.90 (1H, d, H=1.44 Hz, methylene dioxy-H), 6.31 (1H, dd, J=15.2, 3.0 Hz, H-5), 6.87 (1H, dd, J=15.2, 8.2 Hz, H-4), 3.95 (1H, d, J=6.0 Hz, H-2), 3.71 (1H, m, H-3), 3.48 (4H, m, piperidine-H), 1.60 (6H, m, piperidine-H); MS m/z (%): 301 (M^+, 5), 83 (100); UV (EtOH) λ_{max} 230, 207 nm characteristic of substituted styrene system suggests that the double bond adjacent to the carbonyl is involved in the epoxidation.

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