Chemoenzymatic synthesis of derivatives azoles by lipase from Pseudomonas fluorescens

Irlon M. Ferreira* and André L. M. Porto

1Laboratório de Química Orgânica e Biocatálise, Instituto de Química de São Carlos, Universidade de São Paulo, Avenida João Dagnone, 1100, 13563-120, São Carlos, SP, Brazil.

*irlon@iqsc.usp.br

Keywords: Chemo-enzymatic resolution, biocatalysis.

INTRODUCTION

Chiral alcohols are important intermediates in the synthesis of many pharmaceuticals including biologically active compounds. Among these, chiral β-halo aryl alcohols can be considered versatile intermediates in organic synthesis as potential synthetic precursors of pharmaceutically important molecules.1

RESULTS AND DISCUSSION

We synthesized the racemic alcohols (1a-e) using NaBH₄ in methanol (0 °C) by agitation (1h). In flask of 5 mL containing hexane (1 mL), vinyl acetate (0.25 µL) and Pseudomonas fluorescens (20 mg) was added 20 mg of the appropriate rac-alcohol (1a-e). The reaction mixture was stirred on a rotary shaker (32 °C, 130 rpm) and monitored every 24 h by TLC. After this time, the mixture was filtered and the solvent evaporated. Analysis of conversion and enantiomeric excess were done by GC-FID using chiral column (Table 1).

Table 1: Enzymatic kinetic resolution of halo-2-phenylethanol (1a-e) by lipase from P. fluorescens.

| Entry | Substrate | t (h) | ε (%) | e.e (%) | ε' (%) | ε'

| 1a | OH | 96 | 50 | 99 | 94 | 100 |
| 1b | OH | 96 | 49 | 98 | 99 | 100 |
| 1c | OH | 120 | - | - | - | - |
| 1d | OH | 96 | 50 | 98 | 99 | 100 |
| 1e | OH | 48 | 49 | >99 | 98 | 100 |

Then the residue was purified by silica gel column chromatography using hexane/ethyl acetate (9/1) as eluent and analyzed by NMR spectroscopy to confirming the products obtained.

Enzymatic resolution of rac-alcohols (1a-e) by lipase P. fluorescens showed excellent results with high enantiomeric excesses (98-99%), conversions of 48-50% and selectivity E= >200. The alcohol 1d was not converted to acetylated product with lipase from P. fluorescens at 120 h.

To emphasize the importance of this synthetic methodology, 2a and 3a were transformed into enantiopure epoxides (4 and 5) for obtaining derivatives of miconazole. The transformation of the alcohol 2a and 3a into enantiopure epoxides (4 and 5) was carried out by cyclization of the halohydrin using NaOH in ethanol (2mL) at room temperature for 1 h. The extraction was carried out with the addition of a solution of 6M NaHCO₃ (3 mL), saturated solution NaCl (5 mL) and ethyl acetate (3 x 20 mL)² (Scheme 1). The conversion and enantiomeric excesses were determined by GC-FID using chiral column.

CONCLUSION

Enzymatic resolution of halo-2-phenylethanol (1a-e) in the presence of P. fluorescens was efficient for obtaining of enantiopure as agents antifungal derivatives of azoles.

ACKNOWLEDGEMENTS

The authors acknowledge the financial support for CNPq and FAPESP.

REFERENCES