Chemoenzymatic synthesis of derivatives azoles by lipase from *Pseudomonas fluorescens*

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

[1]Laboratório 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

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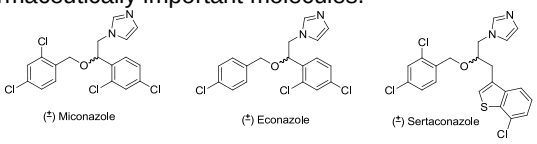
INTRODUCTION

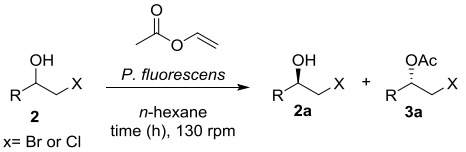
Chiral alcohols are important intermediates in the synthesis of many pharmaceuticals including biologically active compounds. Among these, chiral *β*-halo aryl ethanols can be considered versatile intermediates in organic synthesis as potential synthetic precursors of pharmaceutically important molecules.[1]

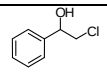
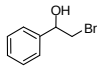
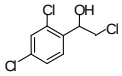
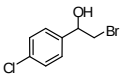
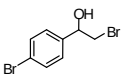


RESULTS AND DISCUSSION

Were synthesized the racemic alcohols (**1a-e**) using $NaBH_4$ in methanol (0 ºC) 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 ºC, 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.*



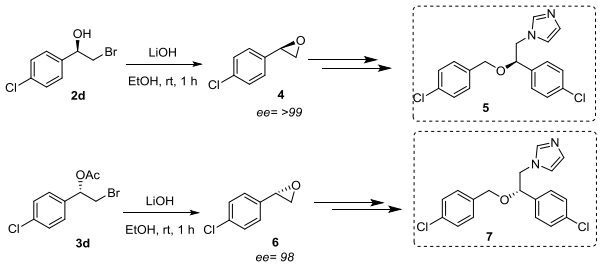
Entry	Substrate	*t* (h)	*c*[a] (%)	*e.e*[c] (2a)	*e.e*[c] (3)	*E*[d]
1a		96	50	99	94	>200
1b		96	49	98	>99	>200
1c		120	-	-	-	-
1d		96	50	98	>99	>200
1e		48	49	>99	98	>200

[a]General conditions: Substrate (20 mg), lipase (20 mg), vinyl acetate (25 µL; 0.25 mmol), *n*-hexane (1 mL), 32 °C, 130 rpm, (-)no reaction. [b]Determined by chiral GC analysis. [d]Conversion: c) eeS/(eeS + eeP). [e]E = {ln[eeP(1 - eeS)]/(eeP + eeS)}/{ln[eeP(1 + eeS)]/(eeP + eeS)}.

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*-alcohos (**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, **2d** and **3d** were transformed into enantiopure epoxides (**4** and **5**) for obtaining derivatives of miconazole. The transformation of the alcohol **2d** and **3d** into enantiopure epoxides (**4** and **5**) was carried out by cyclization of the halohydrine using NaOH in ethanol (2mL) at room temperature for 1 h. The extraction was carried out with the addition of a solution of 6M $NaHCO_3$ (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.



Scheme 1: Synthesis of enantiopure epoxides from resolved alcohols (**2d-3d**)

CONCLUSION

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

ACKNOWLEDGEMENTS

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REFERENCES

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[2]Juan Mangas-Sanchez; *et. al. J. Org. Chem.* **2011**, *76*, 2115–2122.