Green methodologies for the synthesis of α-hydroxycyclohexanone.


Abstract
Water-based reaction and biocatalysis were applied to synthesize racemic and enantioenriched α-hydroxycyclohexanone. .

Key words: Green chemistry, α-hydroxyketone, Biocatalysis, Natural products.

Introduction
α-hydroxyketones (1) are important building blocks for the synthesis of several chemical and pharmaceutical compounds.

Image 1. α-hydroxyketones

These compounds can be obtained using diverse methodologies. However, most of them do not follow the Principles of Green Chemistry. Therefore, this work aims to synthesize racemic and enantioenriched α-hydroxycyclohexanone (2) using green methodologies, such as Biocatalysis and organic reactions in aqueous environment.

Results and Discussion
Racemic α-hydroxycyclohexanone (2) was synthesized using Onomura’s methodology. This procedure is based on the selective oxidation of vicinal diols using KBrO₃ and KHSO₄ in water (Scheme 1). In this reaction the oxidant bromo-species, such as HBrO₂, HBrO, HBr, Br₂ and Br⁺, were generated in situ in aqueous medium, corroborating with the green principles.

Image 2. 1,2-dihydroxycyclohexane (3) oxidation using KBrO₃ and KHSO₄.

The racemic α-hydroxyketone (2) was obtained as a yellow oil with 26% yield, and characterized by GC-MS and ¹H and ¹³C NMR. The low yield can be rationalized by claiming the overoxidation of 2. Alternatively, α-hydroxycyclohexanone (2) was produced via biocatalysis using styrene oxide (4) as substrate and Bacillus pumilus whole cells as biocatalyst (Scheme 2).

Scheme 2. Cyclohexene oxide (4) biotransformation catalyzed by Bacillus pumilus whole cells. EH: epoxide hydrolase, ADH: dehydrogenase.

The biotransformation of cyclohexene oxide (4, 1 mg/mL) was conducted in borate buffer (pH 7.4, 50 mM) at 28 °C and 200 rpm. α-hydroxycyclohexanone (2) was obtained as sole product after 48 h of reaction. Trace amounts of diol (3) was detected with 24 h, which indicates that the biotransformation reaction involves at least two steps: 1) styrene oxide (4) hydrolysis catalyzed by an epoxide hydrolase (EH) and 2) diol 3 dehydrogenation catalyzed by alcohol dehydrogenase (ADH).

The biocatalytic product was also fully characterized by GC-MS and NMR. Enantiomeric excess was determined by chiral GC-FID, revealing that α-hydroxyketone (3) was produced in 85% ee.

Further studies will be developed in order to determine the absolute configuration of the α-hydroxycyclohexanone. Additionally, these two green methodologies will be evaluated for the efficient production of additional α-hydroxyketones of interest.

Conclusions
In this work, a water-based organic reaction and a biocatalytic methodology were successfully applied to the synthesis of α-hydroxycyclohexanone. The biotransformation of cyclohexene oxide into 2 by B. pumilus whole cells is certainly encouraging and shall be applied to other molecules of interest.

Acknowledgement
FAPESP (2011/51278-0, 2014/22967-3), CNPq, ANP-Petrobrás.


DOI: 10.19146/pibic-2016-50927

XXIV Congresso de Iniciação Científica da UNICAMP