Green methodologies for the synthesis of α-hydroxycyclohexanone.

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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.

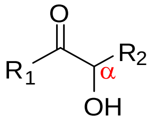


Image 1. α-hydroxyketones

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 enatioenriched 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 KBrO$_3$ and KHSO$_4$ in water (Scheme 1). In this reaction the oxidant bromo-species, such as HBrO$_2$, HBrO, HBr, Br$_2$ and Br$^+$, were generated *in situ* in aqueous medium, corroborating with the green principles.

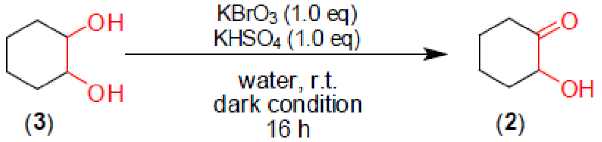
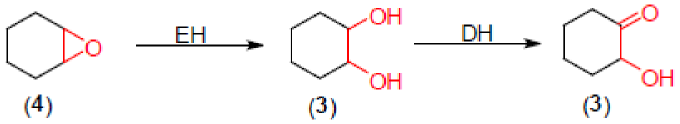


Image 2. 1,2-dihydroxycyclohexane (**3**) oxidation using KBrO3 and KHSO4 .

The racemic α-hydroxyketone **(2)** was obtained as a yellow oil with 26% yield, and characterized by GC-MS and ^{1}H and ^{13}C 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 ºC 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.

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