

Green methodologies for the synthesis of α -hydroxycyclohexanone

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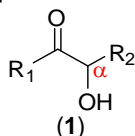
Palavras Chave: Green chemistry, α -hydroxyketone, Biocatalysis, Natural products.

Abstract

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

Introduction

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

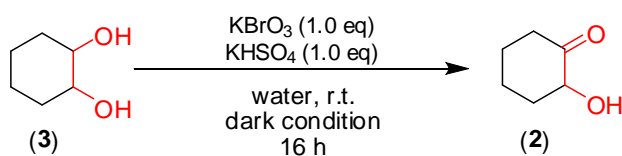


These compounds can be obtained using diverse methodologies. However, most of them do not follow the Principles of Green Chemistry.

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 KBrO_3 and KHSO_4 in water (Scheme 1). In this reaction the oxidant bromo-species, such as HOBrO_2 , HOBrO , HOBr , Br_2 and Br^+ , were generated *in situ* in aqueous medium, corroborating with the green principles.

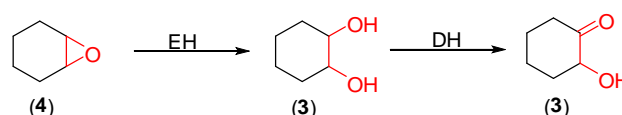


Scheme 1. 1,2-dihydroxycyclohexane (**3**) oxidation using KBrO_3 and KHSO_4 .

The racemic α -hydroxyketone **2** was obtained as a white cristal solid with 26% yield, and characterized by GC-MS and ^1H 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. Styrene oxide (**4**) biotransformation catalyzed by *Bacillus pumilus* whole cells. EH: epoxide hydrolase, DH: dehydrogenase.

The biotransformation of styrene 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 a dehydrogenase (DH).

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.

Conclusion

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

Acknowledgments

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