

CuCl₂/TMEDA mimicking laccase: a mild oxidative dimerization of piperidines

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ABSTRACT

This work investigates the oxidative dimerization of 4-substituted piperidines aiming the formation of *N,N* dimeric bipiperidines by using CuCl₂/TMEDA as a laccase biomimetic. Analyzing the results obtained from both copper complex and laccase oxidation systems, it was possible to obtain the derived product in good yields in addition to a more sustainable pathway if compared to literature.

Keywords: piperidine, laccase, CuCl₂/TMEDA, oxidation, *N,N*-bipiperidine.

Introduction

Nitrogenated heterocycles are widely present in drugs, chemicals and natural compounds and possess great ability in modulating essential properties (1). Piperidine stands out as an important subunit in a variety of bioactive compounds. The diversity of substitutions in the piperidine ring allows the production of molecules with varied applications in Medicinal Chemistry (2). Although the use of laccase as a biocatalyst for the oxidation of oxygenated compounds is known (3), its use for the oxidation of nitrogenated substrates is still unexplored in literature. Laccase, a multicopper oxidase involved in free radical reactions, showed unprecedented potential as copper mediating reactions. Herein, we will present the investigation of CuCl₂/TMEDA complex as a laccase biomimetic, and its ability to generate the same products, suggesting promising and sustainable pathways for the synthesis of bis *N,N* compounds.

Experimental

4-methylpiperidine was used as a standard substrate for the screening of the conditions. Thus, the chemical synthesis of 4,4'-dimethyl-*N,N*-bipiperidine started by adding the CuCl₂/TMEDA catalyst at 10 mol% in a 150 mM solution of 4-methylpiperidine in DCM. The enzymatic synthesis was performed by adding laccase (6 mg/mmol of substrate) in a 150 mM solution of 4-methylpiperidine in *n*-hexane. Both the reactions were conducted at room temperature for four days. Purification was performed by recrystallization from acetone/ethyl acetate 4:1, resulting in a yield of 42% for CuCl₂/TMEDA and 75% for laccase.

Results and discussion

As can be seen in Figure 1, the oxidation of 4-methylpiperidine yields a symmetric compound with only 4 distinct carbons in the ¹³C NMR. In order to confirm the structure, the compound was subjected to other NMR's experiments, and spectroscopic and spectrometric analysis.

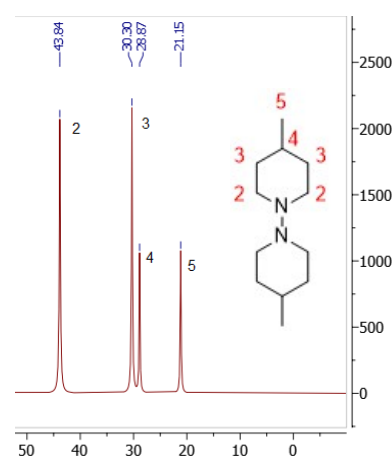


Figure 1. ¹³C NMR of the bipiperidine.

Conclusions

The results demonstrate that both catalytic methods are capable of promoting the oxidative dimerization of 4-methylpiperidine, forming 4,4'-dimethyl-*N,N*-bipiperidine. The similarity between the obtained products reinforces the potential of the chemical catalyst as a laccase mimetic, not only in the oxidation of alcohols, but also in new transformations involving amines. As a perspective, we intend to explore the versatility of these approaches for the creation of a library of piperidine derivatives with bioactive potential.

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References

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