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An efficient method for the transformation of naturally occurring monoterpenes into amines through rhodium-catalyzed hydroaminomethylation

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Dedicated to Professor Christian Bruneau on the occasion of his 60th birthday.

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ABSTRACT

The hydroaminomethylation (hydroformylation/reductive amination) of the naturally occurring monoterpenes, *i.e.*, limonene, camphene, and β-pinene, was studied having as condensation counterparts the amines di-n-butylamine, morpholine or n-butylamine. Moderate to good yields (75–94%) were obtained employing $[Rh(cod)(\mu\text{-}OMe)]_2$ as pre-catalyst in the presence or not of triphenylphosphine or tribenzylphosphine as ancillaries in toluene, at 100 °C and 60 bar of an equimolar mixture of carbon monoxide and hydrogen. Some of the hydroaminomethylation products derived from limonene have biological activity and the products derived from camphene and β-pinene are new.

1. Introduction

Hydroformylation/reductive amination, also known as hydroaminomethylation (HAM), is the catalytic functionalization of a C–C double bond that leads to homologous amines in a one-pot procedure. Therefore, HAM is a highly efficient, environment friendly reaction with good atom economy, as the only byproduct intrinsically formed is water. HAM involves the metal-catalyzed hydroformylation of the double bond, the condensation of the resulting aldehydes with an amine to form enamines (or imines if a primary amine is used as counter-part), followed by their metal-catalyzed hydrogenation, as exemplified in Schemes 1–3. These reactions occur concomitantly and, although not always acknowledged, HAM is within the scope of tandem catalysis, in which two or more catalytic cycles are operating simultaneously [1]. The window for parameter optimization to achieve good activity and selectivity is usually narrower than for a single-step catalyzed reaction. The careful choice of reaction conditions is critical because conditions that may be optimal for one catalytic cycle may be deleterious to another [2].

Although known for a long time [3], only recently, with important contributions of Eilbracht [4–21] and Beller [22–31], has HAM gained importance in the synthesis of more complex molecules, such as pharmaceuticals and other biologically active substances [24,26,32–34]. The use of special ligands such as diphosphines [28], diphosphites [33], and xanthene-based dipyrrolylphosphines [35] allowed good selectivity control associated with high activity. The development of biphasic systems, in which the catalyst is dissolved in water [36], ionic liquids [37], or multiphase termophilic systems [38], allowed for the easier catalyst recycling, favoring industrial applications.

HAM has also been used in the transformation of natural products bearing a C–C double bond into useful chemicals. For example, unsaturated fatty esters were converted into amino-esters with interesting surfactant properties [14]. The HAM of limonene with morpholine or diethylamine leads to amines that are reported as growth regulators in tobacco plants [39]. Da Rosa et al. [40] described recently a one-pot, two-step protocol for the HAM of R-(+)-limonene with various amine counterparts. The products were tested against *Leishmania (V.)braziliensis* and some of them demonstrated better *in vitro* activity than the standard drug pentamidine. Two promising new anti-*T. cruzi* limonene derivatives have also been identified [41].

Pursuing our goal to transform natural products that can be extracted from renewable crops in large amounts into useful or potentially useful new chemicals [42–51], herein we present the results of the hydroaminomethylation of limonene, camphene, and β-pinene, having as condensation

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