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One-pot synthesis of secondary and tertiary amines from R(+)-limonene by tandem hydroformylation/reductive amination (hydroaminomethylation)

Cedric S. Graebin [a], Vera Lucia Eifler-Lima [a], Ricardo G. da Rosa [b,*]

[a] *Laboratório de Síntese Orgânica Medicinal, Faculdade de Farmácia, Universidade Federal do Rio Grande do Sul, Avenida Ipiranga 2752, lab. 704, Porto Alegre 90610-000, Brazil*

[b] *Laboratório de Catálise por Metais de Transição, Instituto de Química, Universidade Federal do Rio Grande do Sul, Avenida Bento Gonçalves 9500, Sala K-104A, Brazil*

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Abstract

In this work, we were able to synthesize, in good isolated yields, seven R(+)-limonene derived amines (five of that described for the first time) employing a rhodium catalysed hydroaminomethylation reaction. This protocol consists in an one-pot three step reaction: double bond hydroformylation, aldehyde/amine condensation and imine/enamine hydrogenation. Hydroaminomethylation, besides the high yields, has a high atom economy because just 1 mol of water is wasted per mol of limonene. Due to our catalytic optimizations, the reaction time was reduced from 48 h (described in the literature) to 10–24 h, as well as limonene isomerization was strongly minimized by the triphenylphosphine added.

Keywords: Limonene; Hydroformylation; Hydroaminomethylation; Terpenes; Secondary amines; Tertiary amines

1. Introduction

Limonene is a main constituent in the essential oil of citrical plants. In nature it is abundant and available in both enantiomeric forms, R(+)-limonene and S(−)-limonene. This and other terpenes have an important role in cosmetics industry. From a chemical point of view, this terpene is very versatile because it presents two double bonds that can be selectively converted in several functional groups. The use of limonene as a building block in organic synthesis is well established in the syntheses of others systems or as a chiral auxiliary in asymmetric synthesis [1,2].

Hydroaminomethylation is a tandem reaction consisting of a one-pot hydroformylation/reductive amination where the same catalyst is responsible for the hydroformylation of the double bond and for the final hydrogenation of the imine/enamine intermediate [3–5]. In this reaction, the hydroformylation is made in the presence of a primary or secondary amine. The aldehyde formed reacts with this amine to obtain the imine or enamine, and then this intermediate is reduced by the catalyst to form a secondary or tertiary amine as the final product.

Limonene **1** has been already hydroaminomethylated with secondary amines [6], and some of them were patented for its use as tobacco growth inhibitors using the aldehyde intermediate as starting material [7,8]. In this work we report improvements in the hydroaminomethylation protocol of limonene with these secondary amines, the synthesis of novel products with primary amines and we briefly discuss some of the findings, taking in account the steric and electronic features of the amine substrates.

* Corresponding author. Tel.: +55 51 3308 7318; fax: +55 51 3308 7304.
E-mail address: ricardo.gomes@ufrgs.br (R.G. da Rosa).

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2. Experimental

2.1. General experimental procedures

^{1}H and ^{13}C NMR spectra were obtained in a INOVA-300 spectrophotometer with standard pulse sequences operating at 300 MHz in ^{1}H NMR and 75 MHz in ^{13}C NMR, using $CDCl_3$ as solvent. Chemical shifts are reported as δ values (ppm) relative to TMS (0.0 ppm). Gas chromatography was performed in a Shimadzu model GC-17A instrument with FID detector and equipped with a DB-5 (30 m × 0.25 mm) column. The carrier gas was hydrogen with a flux of 1.1 mL/min. The following method was used: sample injection = 0.5 μL; initial column temperature = 50 °C; heating rate = 10 °C /min; final temperature = 250 °C; final temperature hold = 10 min (total method time = 30 min). Mass spectrometry was performed in a Shimadzu model CGMS-QP5050 with resolution range from 45 to 400 daltons, in SCAN mode (70 eV), coupled with a Shimadzu model GC-17A gas chromatograph equipped with a DB-17 (30 m × 0.25 mm) column. The carrier gas was Helium with a flux of 1.4 mL/min. The method was the same as detailed in the gas chromatography. The mass spectrometry results are reported as the M/z ratio with the respective relative abundance in parenthesis. The M^+ symbol indicates that the peak is the molecular ion of the compound.

2.2. General procedure for hydroaminomethylation of limonene

A stainless steel autoclave reactor was charged with a mixture of limonene (1.0 mL, 1.19 g, 8.73 mmol), $HRh(CO)(PPh_3)_3$ (11.48 mg, 0.0125 mmol, 0.143 mol%), THF (10 mL) and amine substrate under argon atmosphere. The reactor was purged and charged with 20 bar of H_2 and 20 bar of CO (CAUTION! Carbon monoxide is a very toxic gas and its handling must be done in a well ventilated hood) and heated over a heating plate with magnetic stirring and a silicon oil bath at 100 °C for 5 h. After this time the reactor was cooled, depressurized, purged and pressurized with 40 bar of H_2, and heated in the same conditions as above for 14 h. The reactor was cooled, depressurized and the reaction mixture was eluted in a tiny silica-gel column for the remotion of the catalyst. The solvent and the lightweight components of the mixture (limonene, isomerizated products) were removed in vacuo.

2.2.1. 3-(4-methylcyclohexen-1-yl)-N-propyl-1-butanamine **2a**

Amine substrate: *n*-propylamine (0.8 mL, 9.6 mmol). Hydrogenation step time: 5 h. The product was isolated by remotion of the lightweight components (limonene, amine substrate, isomerizated products) in a high vaccum pump. Yield: 85%. Mass spectrometry: 209.30 (M^+, 0.82). ^{1}H NMR: 0.85 (3H, m), 0.92 (3H, t, $J = 7.48$ Hz), 1.35 (m), 1.5 (m, $J = 7.5$ Hz), 1.65 (3H, s), 1.95 (3H, s), 2.57 (2H, t, $J = 7.5$ Hz), 2.67 (2H, m), 5.38 (1H, s). ^{13}C NMR (mixt. of diastereomers): 11.8, 15.9, 16.3, 23.2, 23.4, 26.9, 27.5, 30.8, 34.3, 34.6, 35.2, 35.3, 38.4, 38.6, 48.3, 48.4, 52, 121, 133.9.

2.2.2. 3-(4-methylcyclohexen-1-yl)-N-isopropyl-1-butanamine **2b**

Amine substrate: *i*-propylamine (0.82 mL, 9.6 mmol). Hydrogenation step time: 10 h. The product was isolated by acid–base extraction and fractionated distillation of the extract. Yield: 50%. Mass spectrometry: 209.25 (M^+, 3.98). ^{1}H NMR: 0.86 (3H, m, $J = 6.4$ Hz), 1.06 (6H, d, $J = 6.3$ Hz), 1.3 (6H, m), 1.63 (3H, s), 1.7 (3H, m), 1.95 (3H, m), 2.6 (2H, m), 2.8 (1H, m(5), $J = 6.3$ Hz), 5.37 (1H, s). ^{13}C NMR (mixt. of diastereomers): 15.8, 16.2, 22.7, 22.8, 23.4, 25.4, 26.8, 27.4, 29.2, 30.7, 30.8, 34.4, 34.7, 35.3, 35.4, 38.3, 38.6, 45.7, 48.7, 120.9, 133.7.

2.2.3. 3-(4-methylcyclohexen-1-yl)-N-benzyl-1-butanamine **2c**

Amine substrate: benzylamine (0.96 mL, 8.73 mmol). Hydrogenation step time: 14 h. The product was isolated by fractionated distillation of the dried reactional mixture. Yield: 44%. Mass spectrometry: 257.29 (M^+, 42.22). ^{1}H NMR: 0.84 (3H, m), 1.35 (4H, m), 1.65 (3H, s), 1.7 (2H, m), 1.8 (2H, m), 1.95 (3H, m), 2.63 (2H, m), 3.8 (2H, s), 5.38 (1H, s), 7.23 (2H, m), 7.32 (3H, m). ^{13}C NMR (mixt. of diastereomers): 15.9, 16.3, 23.4, 25.4, 26.97, 27.5, 29.3, 30.8, 30.9, 34.1, 34.4, 35.1, 35.3, 38.4, 38.6, 47.67, 47.71, 54, 120.9, 126.9, 128.1, 128.2, 128.3, 128.4, 133.9, 140.2.

2.2.4. 3-(4-methylcyclohexen-1-yl)-N-piperidinyl-1-butanamine **2d**

Amine substrate: piperidine (0.95 mL, 9.6 mmol). An excess of PPh_3 (0.0875 mmol) was added in the reaction. Hydrogenation step time: 5 h. The product was isolated by remotion of the lightweight components of the mixture (limonene, piperidine, isomerizated products) in a high vaccum pump. Yield: 80%. Mass spectrometry: 235.25 (M^+, 6.18). ^{1}H NMR: 0.85 (3H, m), 1.4 (6H, m), 1.6 (4H, m), 1.65 (3H, s), 1.7 (3H, m), 1.95 (3H, m), 2.3 (2H, m), 2.4 (4H, m), 5.39 (1H, s). ^{13}C NMR (mixt. of diastereomers): 15.95, 16.3, 23.4, 24.3, 25.4, 25.8, 26.9, 27.5, 29.2, 30.8, 30.85, 30.97, 35.8, 35.9, 38.3, 38.6, 54.6, 57.9, 120.9, 133.8.

2.2.5. 3-(4-methylcyclohexen-1-yl)-N-morphonyl-1-butanamine **2e**

Amine substrate: morpholine (0.84 mL, 9.6 mmol). Hydrogenation time: 5 h. The product was isolated by remotion of the lightweight components of the mixture (limonene, morpholine, isomerizated products) in a high vaccum pump. Yield: 79%. Mass spectrometry: 237.25 (M^+, 1.69). ^{1}H NMR: 0.9 (3H, m), 1.3 (4H, m), 1.65 (3H, s), 1.7 (3H, m), 1.95 (3H, m), 2.4 (3H, m), 2.5 (4H, s), 3.7 (4H, t, $J = 4.7$ Hz), 5.38 (1H, s). ^{13}C NMR (mixt. of diastereomers):15.8, 16.3, 23.3, 25.3, 26.8, 27.4, 29.1,