Journal of Molecular Catalysis A: Chemical 294 (2008) 82–92

Contents lists available at ScienceDirect

Journal of Molecular Catalysis A: Chemical

journal homepage: www.elsevier.com/locate/molcata

Rhodium-catalyzed carbonylation of allylaminoalcohols: Catalytic synthesis of *N*-(2-hydroxy-alkyl)-gamma-lactams and bicyclic oxazolidines

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ARTICLE INFO

Article history:
Received 2 June 2008
Received in revised form 8 August 2008
Accepted 12 August 2008
Available online 19 August 2008

Keywords:
Aminoalcohols
Rhodium–carbonylation mechanism
Lactams
Oxazolidines
Limonene

ABSTRACT

Gamma-lactams and bicyclic oxazolidines are important structural frameworks in both synthetic organic chemistry and related pharmacological fields. These heterocycles can be prepared by the rhodium-catalyzed carbonylation of unsaturated amines. In this work, allylaminoalcohols, derived from the aminolysis of cyclohexene oxide, styrene oxide, (*R*)-(+)-limonene oxide, and ethyl-3-phenyl-glicidate, were employed as substrates. These allylaminoalcohols were carbonylated by employing $RhClCO(PPh_3)_2$ as a precatalyst under varying CO/H_2 mixtures, and moderate to excellent yields were obtained, depending on the substrate used. The results indicated that an increase in the chelating ability of the substrate (–OH and –NHR moieties) decreased the conversion and selectivity of the ensuing reaction. Additionally, the selectivity could be optimized to favor either the γ-lactams or the oxazolidines by controlling the CO/H_2 ratio. A large excess of CO provided a lactam selectivity of up to 90%, while a H_2-rich gas mixture improved the selectivity for oxazolidines, resulting from hydroformylation/cyclization. Studies of the reaction temperature indicated that an undesirable substrate deallylation reaction occurs at higher temperature (>100 °C). Further, kinetic studies have indicated that the oxazolidines and γ-lactams were formed through parallel routes. Unfortunately, the mechanism for oxazolidines formation is not yet well understood. However, our results have led us to propose a catalytic cycle based on hydroformylation/acetalyzation pathways. The γ-lactams formation follows a carbonylation route, mediated by a rhodium–carbamoylic intermediate, as previously reported. To this end, we have been able to prepare and isolate the corresponding iridium complex, which could be confirmed by X-ray crystallographic analysis.

1. Introduction

Catalytic cyclocarbonylation of allylamines is a well-reported process used to prepare *N*-substituted γ-lactams and pyrrolidines [1–3], where this process has been applied in a number of important fields, such pharmaceutical research [4–8]. In 1990, Jegorov and co-workers first reported the rhodium-catalyzed carbonylation of *N*-alkylallylamines. In the present work, we have observed a remarkable effect of the quantity of H_2 in the gas mixture, which allows the reaction to be conducted under milder conditions than using pure CO [9]. However, the reaction mechanism remains unclear. In 1996, Da Rosa and Sanchez-Delgado proposed reaction pathways that describe the formation of γ-lactams by rhodium-catalyzed cyclocarbonylation of *N*-alkylallylamines [1]. In this proposal, γ-lactams are formed by a cyclocarbonylation reaction, where the fundamental step is the nucleophilic attack of the amine nitrogen atom onto a carbonyl group, generating a metal–carbamoyl species. Along with the γ-lactams, non-carbonylated products were also observed, including pyrrolines and pyrrolidines. The origin of these products suggests that reduction of the lactam carbonyl group has taken place by hydrogenation, followed by dehydration (pyrrolines) or dehydration and pyrroline double bond hydrogenation (pyrrolidines). In agreement with the Jegorov work [9], the authors also observed a promoting effect of H_2, which they attributed to its role in the formation of the active rhodium-hydride species.

Da Rosa and Buffon suggested that two parallel pathways are operative in the formation of lactams and pyrrolines/pyrrolidines. They proposed that lactams are formed through a rhodium–carbamoyl intermediate, as described above. However, the formation of pyrrolines/pyrrolidines should follow a hydroformylation/cyclization step proceeding through a rhodium–acyl

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doi:10.1016/j.molcata.2008.08.005

intermediate [10]. In order to obtain better selectivity for the γ-lactams, and considering that dehydration is the key step in pyrrolines/pyrrolidines formation, these authors employed a THF/water solvent system to study the reaction. Indeed, under these conditions, the γ-lactam selectivity increased from 40% to 90%. The effect of phosphine ligands on the reaction course was also studied in order to obtain further improvements in the catalytic performance. Using ^{31}P NMR, the authors observed that these ligands were completely oxidized by water under these reaction conditions, explaining the absence of a phosphorus ligand effect on the catalytic behavior. Therefore, this suggested that water could replace the phosphines as a ligand in the catalytic process, increasing the selectivity for γ-lactams [11].

The carbonylation/hydroformylation of *N*,*O*-functionalized alkenylamines can produce both lactams and/or fused heterocycles [12–14]. Jackson and co-workers have studied the carbonylation of *N*-alkenyl-1,3-diaminopropanes (alkenyl = allyl or 3-butenyl), which provided fused diazabicyclealkanes and lactams. Selectivity control was achieved by carefully optimizing the gas mixture. As such, a large excess of CO ($CO/H_2 = 9/1$) favored carbonylation, while an excess of H_2 ($CO/H_2 = 1/9$) provided primarily the products of hydroformylation. The phosphine ligand effect on the selectivity was also studied, using ligands bearing different steric hindrances and Lewis basicity. Neither the steric demand nor the Lewis basicity of monodentate ligands presented a clear relationship to the hydroformylation or carbonylation products selectivity. However, chelating phosphines, such as BIPHEPHOS, led to the hydroformylation product selectively. Similar results were reported in the carbonylation of isopropylallylamine and *n*-butylallylamine, these being attributed to the difficulty in the formation of the rhodium–carbamoyl intermediate imposed by the chelating metal–ligand ring [12]. Considering the selectivity obtained using chelating phosphines, Jackson and co-workers recently reported the preparation of diazabicyclealkanes and oxazabicyclealkanes from the hydroformylation of 1,3-diaminepropanes and *N*-alkenylaminethanols [13,14].

In the present work, we have studied the carbonylation of allylaminoalcohols, used to prepare *N*-(2-hydroxy-alkyl)-γ-lactams and oxazolidines. We discuss our efforts to control reaction selectivity, and subsequently rationalize a mechanism for the selective formation of both γ-lactams and oxazolidines. Our approach (Scheme 1) was based on the aminolysis of the following epoxides: cyclohexene oxide, **1**; styrene oxide, **2**; (*R*)-(+)-limonene oxide, **3**; hydrogenated (*R*)-(+)-limonene oxide, **4** and the ethyl-3-phenylglycidate **5**. The aminoalcohols obtained were subsequently carbonylated, providing γ-lactams and oxazolidines as the primary products. We further discuss the influence of the hydroxyl group, and the nucleophilicity of the nitrogen in the ring-closing process. Finally, a catalytic cycle that explains the formation of the obtained oxazolidines is proposed.

2. Experimental

2.1. Materials

$RhClCO(PPh_3)_2$ was prepared as described in literature [15]. THF (Nuclear, P.A.) was distilled over Na/benzophenone under an argon atmosphere. Water was distilled before use. Carbon monoxide (White Martins, 99.5%), hydrogen (White Martins, 99.999%), allylamine (Aldrich, 98%), cyclohexene oxide (Aldrich), styrene oxide (Aldrich), ethyl-3-phenylglycidate (Aldrich) and (*R*)-(+)-limonene-oxide (Aldrich, 97%, mixture of *cis* and *trans*) were used as received. Vaska's complex ($IrCl(CO)(PPh_3)_2$) (Strem) was used as received.

2.2. Aminoalcohols synthesis

Aminoalcohols **1a**, **2a**, **3a**, and **4a** were prepared by an adaptation of the method described by Singaram et al. [16,17]. In a typical experiment, 20 mmol of epoxide, 40 mmol of allylamine, and 30 mmol of water were added to a screw-top schlenk flask. The flask was heated to 80 °C, stirred with magnetic stirbar for 24 h, and purified by acid/base extraction. Allylaminoalcohol **5a** was prepared according to the following protocol: A glass flask was used, to which was added 10 mmol of ethyl-3-phenyl-glicidate, 10 mmol of allylamine, and 50 mL of ethanol. The resulting solution was refluxed for 24 h at 80 °C. Next, the solvent was evaporated, and the product was purified by column chromatography using hexane/ethyl acetate as eluent. The silanization was performed as described in literature [18].

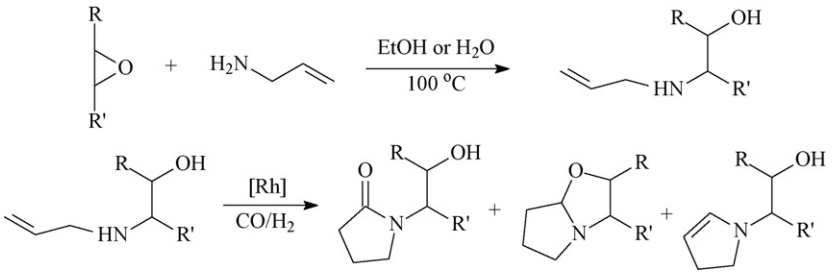
2.3. Catalytic experiments

Catalytic experiments were performed in a 100 mL stainless steel reactor under 20 or 40 bar with varying $CO:H_2$ ratios. The reaction temperature was maintained at 50, 70, or 100 °C, and the solution was stirred with a magnetic stirbar for 24 h. In a typical experiment, 3.00 mmol aminoalcohol (or protected aminoalcohol), 0.015 mmol $RhClCO(PPh_3)_2$, and 20 mL THF were added to a schlenk flask and then transferred *via* cannula to the stainless steel reactor under an argon atmosphere. The reactor was closed, purged with CO, pressurized, and heated in a silicon oil bath at 50 °C. The products were analyzed by GC, GC–MS and purified using column chromatography.

All the isolated products were further analyzed by MS, IR and NMR techniques. The detailed spectroscopy results are available in supplementary material file.

2.4. Iridium–carbamoyl complex synthesis

The iridium analogs for the rhodium–carbamoyl intermediate was synthesized reacting 0.32 mmol (250 mg) of the Vaska's Complex ($IrCl(CO)(PPh_3)_2$) with 16.02 mmol of isopropylallylamine



Scheme 1. Aminolysis of the epoxides followed by allylaminoalcohols carbonylation.