Applied Catalysis A: General 375 (2010) 78–84

Contents lists available at ScienceDirect

Applied Catalysis A: General

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

Pd-catalysed oxidative carbonylation of amino alcohols to *N,N′*-bis(hydroxyalkyl)ureas under mild conditions using molecular oxygen as the oxidant

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ARTICLE INFO

Article history:
Received 23 September 2009
Received in revised form 12 December 2009
Accepted 14 December 2009
Available online 22 December 2009

Keywords:
Oxidative carbonylation
Amino alcohols
N,N′-bis(hydroxyalkyl)ureas
Pd-catalysts

ABSTRACT

A very simple method has been developed for the selective synthesis of symmetrical *N,N′*-bis(hydroxyalkyl)ureas, OC[NH-$(CH_2)_x$-OH]$_2$ (x = 3–6), by oxidative carbonylation of α,ω-amino alcohols [3-aminopropanol (3-AP), 4-aminobutanol (4-AB), 5-aminopentanol (5-APe), 6-aminohexanol (6-AH)] with CO/O_2 mixtures (O_2 = 5 mol%) in the presence of Pd(II)/ligand/NEt_3·HI catalytic systems. The catalytic process takes place under very mild conditions ($p(CO/O_2)$ = 0.1 MPa; 303–333 K). The target products can be isolated in high yield through a very simple and straightforward procedure. The catalytic system can be easily recovered and recycled for several times.

The influence of a few reaction parameters (nature of ancillary ligand and iodide co-catalyst, I/Pd molar ratio, etc.) on the catalytic activity has also been investigated and the main mechanistic features of the catalytic process fully elucidated.

1. Introduction

Oxidative carbonylation of β-amino alcohols to afford oxazolidin-2-ones is a topic of current interest due to the remarkable biological activity exhibited by five-membered cyclic carbamates [1]. Both homogeneous [2] and heterogeneous [3] catalytic systems have been described for this process, which, depending on the nature of the catalyst used, can be accomplished under either mild or drastic conditions. In comparison, oxidative carbonylation of non-vicinal amino alcohols has received much poorer attention, despite its potential for the direct synthesis of *N,N′*-bis(hydroxyalkyl)ureas rather than cyclic carbamates.

N,N′-bis(hydroxyalkyl)ureas are useful compounds which find practical application in several fields [4]. Most of *N,N′*-bis(hydroxyalkyl)ureas can be prepared in a poorly selective way by direct reaction of non-vicinal amino alcohols with phosgene (Scheme 1) [4a,b], a toxic hazardous reagent whose utilization in chemical industry finds larger and larger constraints due to governmental policies for environmental protection. Environmentally more friendly synthetic protocols, based on the reaction of amino alcohols with less toxic phosgene-equivalents (1,1-carbonyldiimidazole, dimethyl ditiocarbonate [5], dimethyl- or diethyl carbonate [6]), are also available, but they often involve multistep procedures aimed at protecting the OH functional group in order to avoid the side-formation of carbamates and carbonates (Scheme 1).

Only recently *N,N′*-bis(hydroxyalkyl)ureas have been prepared by oxidative carbonylation of amino alcohols. Diaz et al. used $W(CO)_6$ as catalyst and stoichiometric amounts of I_2 as the oxidant, under a CO pressure as high as 8 MPa [7]: co-generation of large amounts of iodide salts, as well as tedious work-up of reaction crude, was a serious drawback of the process.

As a part of our studies on the reactivity of key intermediates in the oxidative carbonylation of alcohols [8,9], diols [10] and amines [11], we have recently found that a few L_nPdCl_2 complexes can promote the carbonylation of amino alcohols (NH_2-$(CH_2)_x$-OH) to cyclic carbamates and/or *N,N′*-bis(hydroxyalkyl)ureas and demonstrated that these reactions proceed through the intermediate formation of carbamoyl complexes $L_nPdCl[C(O)NH\text{-}(CH_2)_x\text{-}OH]$ [12]. In general, these species exhibit very modest stability, but the complexes with triphenylphosphine ligand are fairly stable, and have been isolated, characterized and studied for their reactivity. Scheme 2 shows that the complexes $PdCl(PPh_3)_2[C(O)NH\text{-}(CH_2)_x\text{-}OH]$ are thermally unstable and can decompose ($T > 303$ K) by generating a Pd(0)-intermediate, "$Pd(PPh_3)_2$", and a very reactive chloroformamide, ClC(O)NH-$(CH_2)_x$-OH, which, depending on the reaction conditions and the amino alcohol used, can afford either cyclic carbamates or *N,N′*-bis(hydroxyalkyl)ureas. According to whether the decomposition was carried out under N_2 or CO

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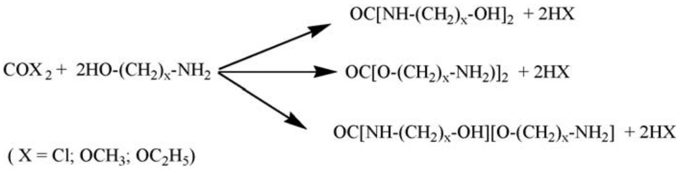
doi:10.1016/j.apcata.2009.12.022



Scheme 1. Carbonylation of amino alcohols with phosgene or phosgene-equivalents.

atmosphere, the palladium(0)-intermediate, "Pd(PPh_3)$_2$", may further react in the reaction mixture by converting, into Pd(0)-carbonyl complexes and/or palladium metal, respectively. Remarkably, in the presence of a suitable oxidant, the latter species can be easily reoxidized to Pd(II), which in the presence of free amino alcohol and CO can regenerate the starting carbamoyl complex, L_nPdCl[C(O)NH-(CH_2)$_x$-OH], allowing, thus, the overall process to proceed in a catalytic way [12] (Scheme 2).

Herein, we report the results obtained with a few tetra-coordinated L_nPdCl_2 complexes [(L = 2,2′-dipyridine (dipy) ($n = 1$); 2-(β-diphenylphosphine)ethylpyridine) (PN) ($n = 1$); PPh_3 ($n = 2$); CH_3CN ($n = 2$)] which, in the presence of NEt_3·HI as co-catalyst and a mixture of CO/O_2 (p(CO/O_2) = 0.1 MPa; O_2 = 5 mol%), act as environmentally benign, highly efficient and stable catalysts for the conversion α,ω-amino alcohols to *N,N′*-bis(hydroxyalkyl)ureas.

2. Experimental

2.1. General

All manipulations were carried out by using standard vacuum-line techniques. Solvents, reactants (amino alcohols, NEt_3, KI), as well as triphenylphosphine and 2,2′-bipyridine (dipy) ligands, were Aldrich or Fluka products and were used as received. PN (2-(β-diphenylphosphino)ethylpyridine) ligand and the Pd-complex $PdCl_2$(PN) were synthesized as described in the literature [13]. The other Pd(II)-complexes, $PdCl_2(PPh_3)_2$ [14], $PdCl_2$(dipy) [15] and $PdCl_2(CH_3CN)_2$ [16], were obtained according to the literature by reacting, at 343 K, a suspension of $PdCl_2$ in CH_3CN with the appropriate ligand. NEt_3·HI was prepared at 273 K, by reacting aqueous HI with an excess of NEt_3 dissolved in CH_2Cl_2. After adding the acid to the amine solution, the organic layer was separated and the salt, NEt_3·HI, was extracted from the aqueous layer with CH_2Cl_2. The CH_2Cl_2 extracts were collected together and from the resulting solution, concentrated to a small volume, white-cream crystal needles of NEt_3·HI were isolated upon addition of Et_2O.

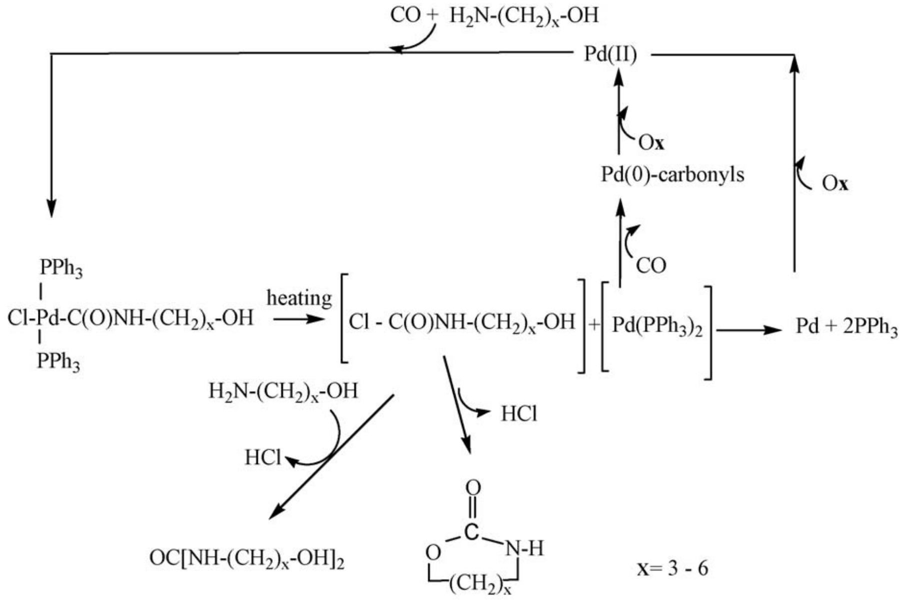
IR spectra were recorded on a Shimadzu IR-Prestige-21 spectrophotometer. GC separations were performed by using a Varian Cromopack CP3800 GC equipped with a CP Sil 8 CB capillary column (30 m, 0.53 mm ID), connected to a FID detector. GC–MS analyses were carried out with a Shimadzu GC 17-A linked to a Shimadzu GC/MS QP5050A selective mass detector (capillary column: HP-5 MS, 30 m). NMR spectra were run on a Bruker AM 500 instrument or a Varian Inova 400 spectrometer. Gas-chromatographic analyses of gas mixtures were carried out on a Porapak Q column (3.5 m), using a Carlo Erba Fractovap GC equipped with a thermal conductivity detector.

2.2. Pd(II)-catalysed oxidative carbonylation of amino alcohols: general procedure

All reactions were carried out in a ≈100 mL glass reactor equipped with a Sovirel cap and a Thorion stopcock. Herein, as an example of typical procedure, the oxidative carbonylation of 4-aminobutanol (4-AB), catalysed by $PdCl_2$(PN)/NEt_3·HI, is described in detail.

CH_3CN (10 mL), NEt_3 (0.5 mL), 4-AB (4.00 mmol), $PdCl_2$(PN) (0.021 mmol) and NEt_3·HI (0.17 mmol; I/Pd = 8 mol/mol) were introduced into the reactor under a N_2 stream. After N_2 removal, the reactor was connected to a flask filled with a CO/O_2 mixture (O_2 = 5 mol%) at ambient pressure (761 mmHg) and temperature (300 K), introduced into an electrical oven equipped with a thermostat and a magnetic stirrer, and allowed to react at 333 K. After 7 h, the volume of consumed gas mixture was measured by means of a gas burette and the solution was analyzed for reactants and products.

The reaction mixture was reacted with pure O_2 at 333 K for 20 min (to oxidize minor amounts of Pd-black formed in the reaction system) and then cooled to room temperature. A white precipitate was obtained which was filtered off, washed with a 2:1 (v/v) Et_2O/CH_3CN mixture, dried *in vacuo* and identified as *N,N′*-bis(4-hydroxybutyl)urea by means of elemental analysis and



Scheme 2. Thermal decomposition of Pd-carbamoyl complexes from amino alcohols and formation of products under oxidative conditions.