Tetrahedron 70 (2014) 6938–6943

Contents lists available at ScienceDirect

Tetrahedron

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

Ring opening of heterocycles containing a C–N double bond: a simple synthesis of imides promoted by acyl palladium species

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ARTICLE INFO

Article history:
Received 31 March 2014
Received in revised form 16 July 2014
Accepted 29 July 2014
Available online 2 August 2014

Keywords:
Imides
Nitrogen heterocycles
Oxygen heterocycles
Palladium
Carbonylation

ABSTRACT

A detailed study on the reactivity of various heterocycles, containing a C–N double bond, with acyl palladium species, generated in situ from allyl or benzyl halides and CO, has been performed. While the cyclic imine 2-methyl-1-pyrroline reacted with acyl-palladium intermediates to give a bicyclic β-lactam, other heterocycles containing a C–N double bond conjugated with a heteroatom (O or N), showed a ring-opening reaction leading to functionalized imides with high structural diversity. Such methodology represents a simple and direct way to prepare structurally complex imides. Moreover, a reaction mechanism, involving cationic intermediates, was also proposed.

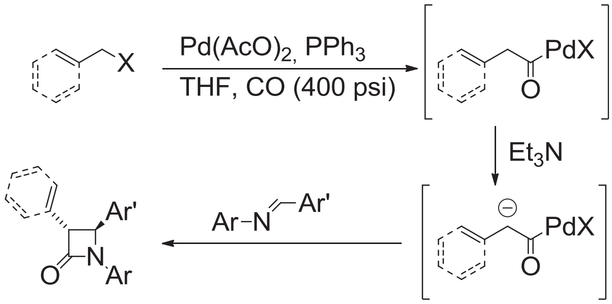
1. Introduction

There is great demand in the field of pharmacology to find different antibiotics that can help overcome the problem of resistance to antibiotic drug therapy. The most common mechanism for resistance to β-lactam antibiotics is the ability of bacteria to produce β-lactamases.[1–5] Therefore there is a great interest among researchers in finding novel β-lactam structures through new synthetic approaches.[6]

We recently reported the synthesis of numerous *trans* β-lactams through the [2+2] cycloaddition between allyl (or benzyl) acyl palladium chlorides (or bromides), prepared 'in situ', and simple aldimines.[7] This methodology is shown in Scheme 1.

A synthetic approach, very similar to that previously described, was proposed by Torii et al. using allyl phosphates.[8,9]

The interest in creating different β-lactam structures, to address and overcome the problem of β-lactamases, has prompted us to examine the palladium-catalyzed [2+2] carbonylative cycloaddition to carbon–nitrogen double bonds when these are contained in cyclic compounds.



Scheme 1. Synthesis of β-lactams via an acyl-palladium intermediate.

With the aim of expanding the scope of the carbonylative coupling reactions between unsaturated halides and imines, we conducted a survey using a series of five- and six-membered heterocycles containing a carbon–nitrogen double bond, Table 1; the results of the Pd-catalyzed carbonylation[10] with allyl and benzyl halides are reported in this work.

2. Results and discussion

Our investigation began with the reaction of 2-methyl-1-pyrroline **1a** and allyl chloride under the conditions previously

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http://dx.doi.org/10.1016/j.tet.2014.07.099
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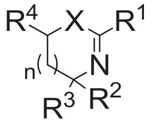
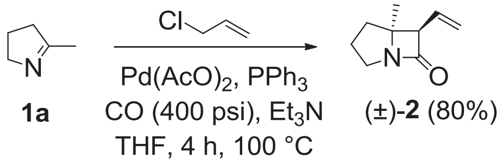
Table 1
Heterocycles, containing a C–N double bond, used in this work



	R^1	R^2	R^3	R^4	X	*n*
1a	Me	H	H	H	CH_2	0
1b	Ph	H	H	H	O	0
1c	Me	Me	Me	H	O	0
1d	Et	Me	Me	H	O	0
1e	Et	H	CH_2Ph	H	O	0
1f	Me	H	H	H	NMe	0
1g	Me	H	H	H	S	0
1h	Me	Me	Me	Me	O	1

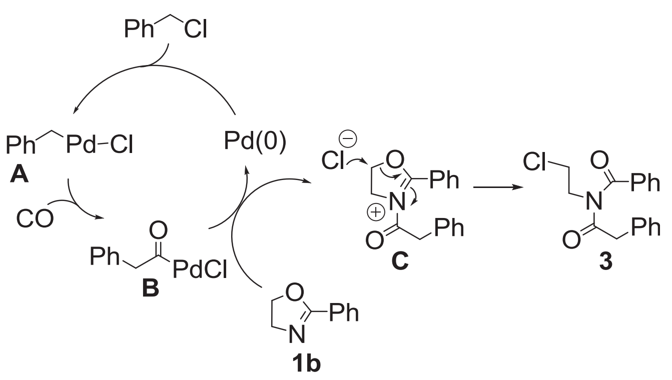
reported for aldimines.[11] Allyl chloride (1.5 mmol), triphenylphosphine (0.08 mmol), $Pd(AcO)_2$ (0.02 mmol), and triethylamine (2.0 mmol) were added to a solution of pyrroline **1a** (1.0 mmol) in THF (15 mL). The solution was placed in an autoclave, suitably purged and pressurized with CO (400 psi), then heated to 100 °C for 4 h. After this time, the autoclave was cooled and carbon oxide discharged and the solution, after filtration, was analyzed by GC and GC–MS. One product was formed and column chromatography on silica gel (eluent: petroleum ether/ethyl acetate 7/3) provided the β-lactam **2** as a pure compound (yield 80%, Scheme 2). The relative configuration of **2** was established via a 2D ^1H–^1H NOESY experiment. This result was in full agreement with what has been previously reported for non-cyclic imines,[11] and therefore we did not investigate further with other acyl palladium derivatives.



Scheme 2. Formation of the bicyclic β-lactam **2**.

We then focused our attention on the different substrates shown in Table 1, featuring a C–N double bond conjugated to an additional heteroatom (O, N or S); as expected, we observed completely different behavior.

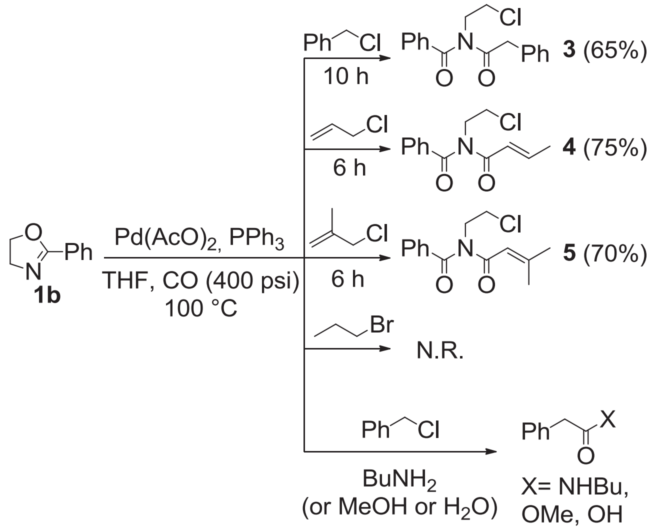
In particular, oxazolines **1b–e** (Table 1), in the presence of an acyl palladium chloride intermediate, like structure **B** depicted in Scheme 3, gave rise to a new ring-opening reaction. When **1b** was reacted with benzyl chloride under a CO atmosphere (400 psi), in the presence of Et_3N (2.0 mmol), with the catalysis of the $Pd(AcO)_2$/PPh_3 system, only one product was formed after 10 h at 100 °C; its isolation was performed by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate 7/3). ^1H NMR, ^{13}C NMR, FT-IR spectroscopy, and GC–MS analyses agreed with the structure of *N*-(2-chloroethyl)imide **3** (yield=63%, Scheme 3). To the best of our knowledge, this result represents the first case of a cationic oxazoline ring-opening promoted by an acyl palladium species generated in situ.



Scheme 3. Proposed mechanism for Pd-catalyzed ring opening of oxazoline **1b** to imide **3**.

This reaction requires Pd(0) whose formation is achieved by in situ reduction of $Pd(AcO)_2$ by PPh_3. The reaction proceeds initially with the formation of the benzyl palladium complex **A**, and then with the insertion of CO generating the acyl-palladium intermediate **B** that reacts with oxazoline **1b**. We postulate that the presence of the oxygen atom in the α-position with respect to the C–N double bond in the oxazoline makes the nitrogen more nucleophilic, favoring the reaction with the acyl palladium chloride and producing the *N*-acyl-2-oxazolinium **C**; the latter, after the nucleophilic attack of a chlorine anion, leads to the formation of the imide **3** (Scheme 3).

Unlike in the case of β-lactams, whose synthesis needs the use of triethylamine,[11] according to the suggested mechanism in Scheme 3, Et_3N seems to be unnecessary for the formation of *N*-(2-chloroethyl)imides. Indeed, the reaction carried out with oxazoline **1b** and benzyl chloride without the use of Et_3N, gave similar results in terms of product and yield (Scheme 4). For this reason, all the other reactions involving the heterocycles **1b–h** were performed without using Et_3N.



Scheme 4. Synthesis of imides **3–5** from oxazoline **1b**. Reagents and conditions: oxazoline **1b** (1.0 mmol), halide (1.5 mmol), $Pd(AcO)_2$ (0.02 mmol), PPh_3 (0.08 mmol), CO (400 psi), THF (15 mL), 100 °C.

The opening of the oxazoline cycle by nitrogen acylation, with benzoyl chloride, was reported by Song et al. for the synthesis of an ambident cyclic ketene-*N*,*O*-acetal[12] and by Dworak in the polymerization of methyl and phenyl oxazoline with carboxylic acid chlorides;[13] while the formation of 2-oxazolinium cationic species was previously hypothesized by Tomalia and Paige.[14]

A similar trend was found in the Pd-catalyzed carbonylation reaction of allyl chloride or methallyl chloride in the presence of oxazoline **1b** obtaining (*E*)-*N*-(2-chloroethyl)-*N*-(2-butenoyl)benzamide **4** or *N*-(2-chloroethyl)-*N*-(3-methyl-but-2-enoyl)benzamide **5**, respectively, with isolation in good yields (Scheme 4). Since