Tetrahedron Letters 57 (2016) 1421–1424

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis of β-enamino acid and heteroaryl acetic acid derivatives by Pd-catalyzed carbonylation of α-chloroimines and 2-chloromethyl aza-heterocycles

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ARTICLE INFO

Article history:
Received 26 December 2015
Revised 5 February 2016
Accepted 9 February 2016
Available online 10 February 2016

Keywords:
α-Chloroimines
β-Enamino esters
β-Enamino amides
Arylacetic acids
Pd-catalyzed carbonylation

ABSTRACT

β-Enamino esters or amides can be synthesized in a single step by a carbonylative coupling of α-chloroimines with alcohols or amines under Pd-catalysis. The methodology has been also applied to the preparation of heteroaryl acetic acid derivatives starting from chloromethyl heteroaromatic rings containing a C—N double bond. The in situ generation of a β-imino acylpalladium species has been proposed as a key step for the process.

Introduction

Palladium catalyzed carbonylation is a powerful tool for synthetic organic chemists because it allows the construction of valuable carbonyl compounds in a single step with efficiency, selectivity, and atom economy. As well as the most palladium mediated C—C bond forming reactions, Pd-catalyzed carbonylation is compatible with a range of functional groups and gives considerable advantages over standard organolithium and Grignard chemistry for the synthesis of aldehydes, acids, esters, and amides.[1]

As part of our previous studies on the carbonylation of α,β-unsaturated halides,[2] we found that treatment of allyl chloride with a series of aliphatic and aromatic alcohols, under CO pressure (27 atm) at 100 °C, in the presence of $Pd(OAc)_2$, NEt_3, and PPh_3, led to a number of β,γ-unsaturated esters after 10 h (Scheme 1).

Conversely, when the reaction time was increased to 20 h, we isolated the conjugated α,β-unsaturated ester as the main product of the reaction (Scheme 1).[3] The observed C—C double bond shift in the product is likely due to thermodynamic reasons. Indeed, α,β-unsaturated esters can benefit of a stabilizing delocalization phenomenon with respect to their β,γ-unsaturated isomers.

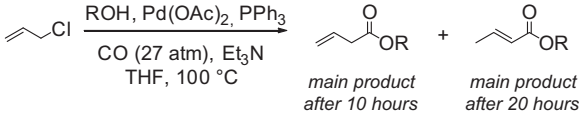
Such a strategy has been previously applied to the synthesis of α,β-unsaturated amides by performing the carbonylation reaction of allylic halides in the presence of amines.[4]

On the basis of these results, we reasoned that the employment of α-chloroimines as α,β-unsaturated substrates for a Pd-catalyzed carbonylation could represent a short way for the formation of β-enamino esters or amides (Scheme 2).

β-Enamino acid derivatives are a class of valuable synthetic intermediates. Therefore, the development of new methodologies for their preparation is desirable for accessing biologically relevant molecules containing or deriving from this structural motif.[5]

Moreover, β-enamino acid derivatives have been shown to be useful building blocks in asymmetric organic synthesis;[6] among them, the noteworthy catalytic enantioselective reduction was pioneered by Noyori to obtain optically active β-aminoacids.[6c]

In addition to the classical condensation between β-keto acid derivatives and amines, the synthesis of β-enamino acid



Scheme 1. Synthesis of unsaturated esters by Pd-catalyzed carbonylative coupling between the allyl chloride and alcohols.

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http://dx.doi.org/10.1016/j.tetlet.2016.02.035
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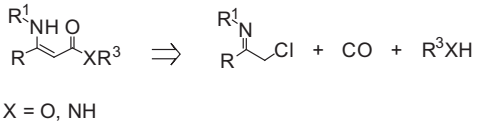


Scheme 2. Retrosynthetic analysis for the preparation of α,β-unsaturated β-aminoacid derivatives from α-chloroimines.

derivatives have been recently obtained by different routes involving the addition of amines to acrylates,[7a] propiolates,[7b–d] by the reaction of imines to activated carbonic acid derivatives,[7e] or by lithiation of 5-phenylthioisoxazolines.[7f]

In this Letter we report a novel *one-pot* synthetic procedure for the preparation of β-enamino esters or amides by a Pd-catalyzed carbonylation of α-chloroimines in the presence of alcohols or amines, respectively.

Results and discussion

The reaction of the imine **2a** with carbon monoxide and methanol, under palladium-catalysis, was chosen as a model experiment (Table 1).

The α-chloroimines **2** were prepared by a direct condensation of the corresponding α-chloroketone **1a–d** (Fig. 1) with an appropriate primary amine in dry Et_2O, according to Taguchi's protocol (Tables 1 and 2).[8]

Unfortunately, any attempt of isolation of α-chloroimines **2a–f**, by column chromatography on silica gel, resulted ineffective since the product was rapidly hydrolyzed back to the corresponding starting α-chloroketone **1** and amine. For this reason, the crude imine **2**, obtained after filtration of the molecular sieves and removal of the solvent under *vacuum*, was used for the carbonylation reaction without any further purification.[9]

We began our investigation by trialing the carbonylative coupling under the following experimental conditions: freshly prepared α-chloroimine **2a** (1.0 mmol), methanol (3.0 mmol), NEt_3 (2.0 mmol), and $Pd(OAc)_2$ (2 mol %) were dissolved in dry THF (15 mL). The resulting solution was placed in an autoclave, under CO pressure (27 atm), and heated at 110 °C for 20 h. Initial results were encouraging: the use of $Pd(OAc)_2$ as catalyst gave the desired β-enamino ester (*Z*)-**3a**[10] in 45% yield (Table 1, entry 1).

Based on our previous experience in the field of carbonylations, we decided to screen different Pd-catalysts and found that Pd $(PPh_3)_4$ was optimal, increasing the yield up to 70% (Table 1, entries 2–4). Control experiments established that a high temperature (110 °C), NEt_3, and THF were all required for a successful reaction (Table 1, entries 5–10).

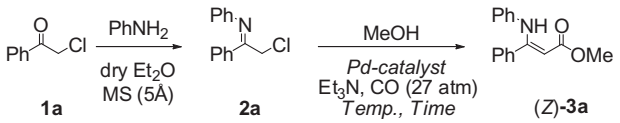
A brief screening of the reaction time and methanol equivalents demonstrated that after only 10 h the product **3a** was already formed; particularly, it was isolated in 63% and 72% yield when 3 and 5 equiv of methanol were used, respectively (Table 1, entries 11 and 12).

As a drawback, it is necessary to point out that the α-chloroimine **2a**, used in the model reaction (Table 1), was found to lose the chlorine atom during the reaction. In fact, beside the target product **3a** we observed the corresponding dehalogenated imine (detected by ^1H NMR and GC–MS on the crude reaction mixture).[11]

With the best conditions in hand (Table 1, entry 12) we examined the scope of the reaction by extending the methodology to a variety of α-chloroimines **2b–f** and aliphatic alcohols or amines (Table 2).

It was found that, in addition to the *C*,*N*-diaryl substituted imine **2a**, also the *N*-alkyl derivatives **2b** and **2c** were successfully carbonylated in the presence of an excess of methanol to afford (*Z*)-β-enamino esters **3b** and **3c** in moderate to good yields (66–85%, Table 2, entries 1 and 2).

Table 1
Optimization of reaction conditions for the model carbonylative coupling between imine **2a** and methanol[a]



Entry	Catalyst	Temp (°C)	Time (h)	Solvent	(*Z*)-**3a** Yield[b] (%)
1	$Pd(OAc)_2$	110	20	THF	45
2	$Pd_2(dba)_3$	110	20	THF	34
3	Pd/C	110	20	THF	20
4	$Pd(PPh_3)_4$	110	20	THF	70
5	$Pd(PPh_3)_4$	90	20	THF	45
6	$Pd(PPh_3)_4$	60	48	THF	20
7	$Pd(PPh_3)_4$	25	48	THF	<5
8	$Pd(PPh_3)_4$	110	20	THF	—[c]
9	$Pd(PPh_3)_4$	110	20	Et_2O	<5
10	$Pd(PPh_3)_4$	110	20	Toluene	18
11	$Pd(PPh_3)_4$	110	10	THF	63
12	$Pd(PPh_3)_4$	110	10	THF	72[d]

[a] Reagents and conditions on 1 mmol scale: α-chloroimine **2a** (1.0 mmol), methanol (3.0 mmol), NEt_3 (2.0 mmol), Pd-catalyst (2 mol %), CO (27 atm), dry THF (15 mL), 110 °C. All reactions were run in duplicate.
[b] Isolated yield after column chromatography on silica-gel.
[c] Reaction performed without NEt_3.
[d] Reaction performed with 5 equiv of MeOH.

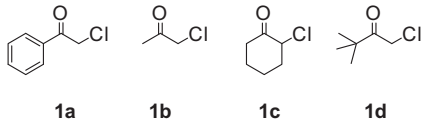


Figure 1. α-Chloroketones used in this study.

We next looked at applying our conditions to *C*-alkyl, *N*-arylimines, such as the derivatives **2d-f** (Table 2, entries 3–5). Pleasingly, products **3d–f** were formed in fairly good to high yields (65–93%), demonstrating that the reaction can be performed also with α-chloroimines containing an exocyclic C—N double bond (Table 2, entry 4) or a bulky group such as a *tert*-butyl as a *C*-substituent (Table 2, entry 5).

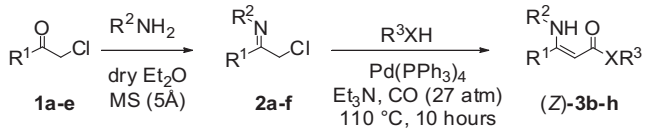
The formation of the methyl esters **3a–f**, as the main products of our carbonylation reactions, can be explained if a β-imino acylpalladium species **A** (Scheme 3) is postulated as an acylating intermediate reacting with methanol. On the basis of this assumption we envisioned that the scope of this reaction could be expanded to the synthesis of β-enamino amides by replacing the alcohol with a suitable amine.

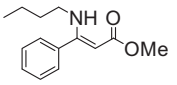
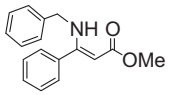
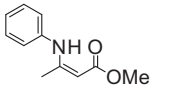
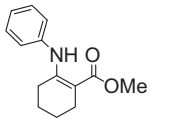
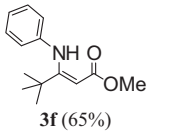
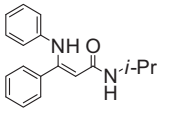
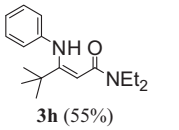
With no further optimization of the reaction conditions, we were pleased to find that when the α-chloroimines **2a** or **2f** were carbonylated in the presence of an excess of isopropylamine or diethylamine, β-enaminoamides **3g** and **3h** were isolated in 85% and 55% yield, respectively (Table 2, entries 6 and 7).

In terms of method limitations, we observed that no carbonylative coupling occurred when either phenol or aniline was employed as a nucleophile (Table 2, entries 8 and 9). In these cases, the dehalogenated imine was the only product detectable by ^1H NMR and GC–MS analyses of the crude mixture.

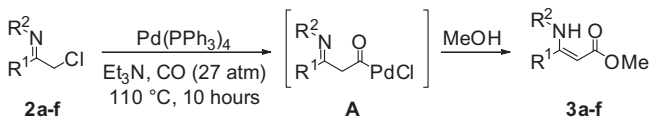
It is noteworthy that all the synthesized products **3a–h** showed a *Z*-configuration.[12] Such high stereoselectivity of the process can be rationalized by considering that the formation of a stabilizing intramolecular hydrogen bond between the enaminic NH and the carbonyl group with the related formation of a six-membered ring is allowed only in the *Z* isomers.[13]

Table 2
Scope of the carbonylative coupling between α-chloroimines **2a–f** and alcohols or amines[a,b]



Entry	Imine **2**	R^1	R^2	R^3	X	Product **3** (Yield %)[c]
1	**2b**	Ph	*n*-Bu	Me	O	 **3b** (85%)
2	**2c**	Ph	Bn	Me	O	 **3c** (66%)
3	**2d**	Me	Ph	Me	O	 **3d** (75%)
4	**2e**		Ph	Me	O	 **3e** (93%)
5	**2f**	*t*-Bu	Ph	Me	O	 **3f** (65%)
6	**2a**	Ph	Ph	*i*-Pr	NH	 **3g** (85%)
7	**2f**	*t*-Bu	Ph	Et_2	N	 **3h** (55%)
8	**2b**	Ph	*n*-Bu	Ph	NH	—
9	**2b**	Ph	*n*-Bu	Ph	O	—

[a] Reagents and conditions on 1 mmol scale: freshly prepared α-chloroimine **2** (1.0 mmol), alcohol or amine (5.0 mmol), NEt_3 (2.0 mmol), $Pd(PPh_3)_4$ (2 mol %), CO (27 atm), dry THF (15 mL), 110 °C, 10 h.
[b] In the case of entry 4, the structure showed in the column R^1 is intended to be as the whole chloroketone and not a substituent.
[c] Isolated yield after column chromatography on silica-gel.



Scheme 3. β-Imino acylpalladium **A**: supposed key intermediate in the carbonylative coupling of α-chloroimines with *O*-nucleophiles.

We then moved on to establish whether the present protocol could be further extended toward the use of unsaturated halides in which the C—N double bond belongs to an aromatic system. To this end chloromethyl-substituted benzothiazole, pyridine, and benzimidazole **4a–c** were employed (Table 3).

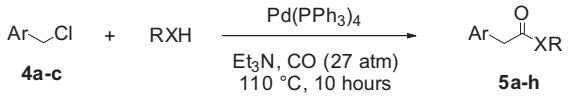
Once **4a** was subjected to the carbonylative coupling with methanol or isopropanol, under the reaction conditions optimized for **2a**, it successfully afforded the expected heteroaryl acetate **5a** and **5b** in 87% and 80% yield, respectively (Table 3, entries 1 and 2).

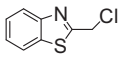
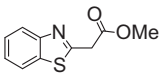
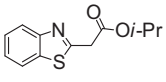
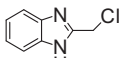
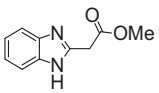
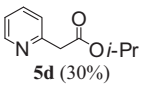
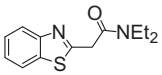
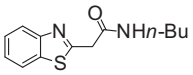
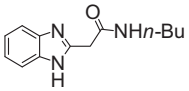
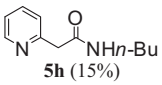
Similarly, we found that the efficiency of the methodology remained unchanged when benzimidazole derivative **4b** was carbonylated in the presence of an excess of methanol, to produce the ester **5c** in 85% yield (Table 3, entry 3).

In contrast, when 2-chloromethyl pyridine **4c** was subjected to the coupling with isopropanol, we isolated the 2-pyridylacetate **5d** in only 30% yield (Table 3, entry 4). To explain such a dramatic decrease in the yield, we hypothesize that the pyridine ring can act as a nucleophile reacting with the acylpalladium intermediate **A**.

The reaction could be also applied to the synthesis of heteroaryl acetamides when the chlorides **4a–c** were subjected to our carbonylation procedure in the presence of primary and secondary amines (Table 3, entries 5–8). Indeed, benzothiazole and benzimidazole systems well tolerated the methodology leading to the formation of the amides **5e–g** in very good yields (90–96%, Table 3, entries 5–7); unfortunately, the carbonylative coupling between

Table 3
Synthesis of heteroaryl-substituted acetic acid derivatives 5**a–h**[a]



Entry	$ArCH_2Cl$	R	X	Product **5** (Yield %)[b]
1	 **4a**	Me	O	 **5a** (87%)
2	**4a**	*i*-Pr	O	 **5b** (80%)
3	 **4b**	Me	O	 **5c** (85%)
4	 **4c**	*i*-Pr	O	 **5d** (30%)
5	**4a**	Et_2	N	 **5e** (95%)
6	**4a**	*n*-Bu	NH	 **5f** (96%)
7	**4b**	*n*-Bu	NH	 **5g** (90%)
8	**4c**	*n*-Bu	NH	 **5h** (15%)

[a] Reagents and conditions on 1 mmol scale: chloromethyl arene **4** (1.0 mmol), alcohol or amine (5.0 mmol), NEt_3 (2.0 mmol), $Pd(PPh_3)_4$ (2 mol %), CO (27 atm), dry THF (15 mL), 110 °C, 10 h.
[b] Isolated yield after column chromatography on silica-gel.

2-chloromethylpyridine and *n*-butyl amine afforded the product **5h** in only 15% yield (Table 3, entry 8). GC–MS and ^{1}H NMR analyses of the crude mixture showed that, along the desired Pd-catalyzed carbonylation, a competitive nucleophilic attack of butylamine to 2-chlromethylpyridine occurred.[14]

To conclude, we developed a mild and high yielding methodology for concomitant C—C and C—O or C—N bond formation across α-chloroimines or chloromethyl heteroaromatic rings containing a C—N double bond. The reaction provides access to β-enamino acid derivatives and heteroaryl acetic esters or amides, in a single step starting from cheap and readily available starting materials. Further applications of this chemistry are currently being explored in our laboratory.

Acknowledgments

The authors thank the University of Salento and the Consorzio Interuniversitario Nazionale 'Metodologie e Processi Innovativi di Sintesi' (C.I.N.M.P.I.S).

Supplementary data

Supplementary data (synthesis of **2a–f**, **3a–h**, **5a–h** and characterization data for all new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.02.035.

References and notes

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9. The purity grade of crude imines **2a–f** has been ascertained by ^{1}H NMR with the internal standard technique, and measured to be in 80–85% range.
10. (*Z*)-Methyl 3-phenyl-3-(phenylamino)propenoate **3a** is known, and its characterization data resulted in agreement with those reported in the literature (see Supplementary material).
11. A similar reactivity has been found in our laboratory when the carbonylation reaction of α-chloroketones has been examined: see Ref. 2e.
12. The relative configuration of products **3a–h** has been determined by 2D ^{1}H–^{1}H NOESY analyses.
13. The intramolecular hydrogen bond formation (N—H···O=C) for derivatives **3a–h** has been postulated by ^{13}C NMR analysis in analogy to a previously reported work: Fustero, S.; de la Torre, M. G.; Jofre, V.; Carlon, R. P.; Navarro, A.; Fuentes, A. S.; Carrio, J. S. *J. Org. Chem.* **1998**, *63*, 8825–8836.
14. Two by products were found in the crude reaction mixture namely *N*-(pyridin-2-ylmethyl)butan-1-amine and *N*,*N*-bis(pyridin-2-ylmethyl)butan-1-amine.