Preparation of benzolactams by Pd(II)-catalyzed carbonylation of *N*-unprotected arylethylamines

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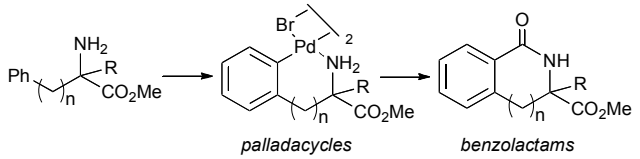
An unprecedented NH_2-directed Pd(II)-catalytic carbonylation of quaternary aromatic α-amino esters to yield 6-membered benzolactams has been developed. The reaction shows a strong bias to 6-membered lactams over 5-membered ones. The steric hindrance around the amino group seems to be pivotal for the success of the process.

The development of selective methods for the direct conversion of carbon-hydrogen bonds into carbon-heteroatom and carbon-carbon reactions remains a critical challenge in organic chemistry. An interesting approach to address this issue involves the use of aromatic substrates that contain coordinating atoms (or directing groups).[1] These ligands bind to the metal center in the first step and a further rearrangement of some atoms allows the C-H bond activation. The factors that influence this well-known cyclometalation reaction are now reasonably well understood.[2]

The transition-metal-catalyzed carbonylation of arenes involving CO gas is also a significant chemical transformation since it not only extends the carbon chain length but it also introduces a synthetically versatile carbonyl group. Arenes were first carbonylated by Fujiwara in 1980 with $Pd(OAc)_2$ under 15 atm of CO using the arene substrates as solvent to obtain carboxylic acids.[3] However, no control over regioselectivity was observed in the case of substituted arenes. This problem has been overcome by different research groups through the directing group approach.[1,4] Thus, Yu *et al* described very recently the palladium acetate-catalyzed carbonylation of anilides to obtain N-acyl anthranilic acids.[4d] In this regard, Orito *et al*, reported in 2004 the direct carbonylation with CO of aromatic C-H bonds in *N*-alkyl-*ω*-arylalkylamines using a $Pd(OAc)_2/Cu(OAc)_2$/air system in toluene solution at 120 ºC, to obtain benzolactams.[4b,5] However, the authors stated that "*carbonylation of primary amines, including benzylic amines or phenylethylamines, under the same conditions, produced no benzolactams but produced ureas in good yields*".‡ Thus, a method for catalyzed C-H activation/carbonylation of primary amines under a CO environment has not been established.

Here we describe the first preparation of benzolactams by palladium acetate-catalyzed aromatic carbonylation of quaternary α-amino α-alkyl esters, by an unprecedented process that uses NH_2 as a directing group.

As part of an ongoing research project on bioorganometallic chemistry,[6] we attempted the cyclometallation of imines RCH=NC(Me)(CH_2Ph)(COOMe) (R = 4-ClC_6H_4 or 2,6-$Cl_2C_6H_3$), derived from quaternary α-amino ester **1a**, with $Pd(OAc)_2$ in toluene or AcOH. Unexpectedly, no imine palladacycle was obtained, but **3a** arising from the metallation of the corresponding free amino ester was isolated after subsequent reaction with LiBr (see Scheme 1). When we applied the same conditions to free amino ester **1a**, palladacycle **3a** was isolated again in 79% yield. We could extend the process to amino esters **1b**, **2a**, and **2b**. These results were unexpected because it is not easy to metallate primary amines,[7] and are in contrast with those obtained from the closely related imines arising from the α-amino acids glycine, alanine, valine and tyrosine methyl esters, which have been metallated in good yields.[6c]



1a, n = 1, R = Me
1b, n = 1, R = Pr
2a, n = 0, R = Me
2b, n = 0, R = Pr

3a, n = 1, R = Me
3b, n = 1, R = Pr
4a, n = 0, R = Me
4b, n = 0, R = Pr

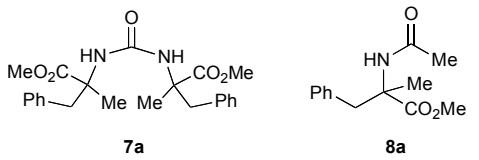
5a, n = 1, R = Me
5b, n = 1, R = Pr
6a, n = 0, R = Me
6b, n = 0, R = Pr

Scheme 1. Stepwise transformation of quaternary α-amino esters **1** and **2** into benzolactams.

These results show that the presence of substituent R in **1** and **2** plays a pivotal role in the metallation reaction, probably due to the beneficial effects of steric bulk in avoiding secondary reactions, but also by the Thorpe-Ingold effect[8,2b] (or *gem*-dimethyl effect) which states that alkyl substituents positioned on the acyclic carbon backbone improve the outcome of organic cyclization reactions. A combination of the different hydrolysis processes¶ that imines undergo and the *gem*-dimethyl effect can explain our experimental findings.

The great tendency showed by these free amino esters to undergo cyclopalladation prompted us to study their palladium-catalyzed NH_2-directed carbonylation at low pressure. First, we confirmed that palladacycle **3a** was easily carbonylated to benzolactams **5a** with CO (1 atm) in different solvents even at r.t. Then we investigated the palladium acetate-catalyzed carbonylation of racemic amino acid **1a**, using $Cu(OAc)_2/O_2$ as the oxidant in toluene. Unfortunately, urea **7a** (Fig. 1) was obtained in different experimental conditions but not the expected benzolactam **5a**. Since a strong accelerating effect in some reactions catalyzed by $Pd(OAc)_2$ in AcOH has been reported,[9] we changed to this

solvent. Fortunately, we obtained the desired lactam **5a** but it was contaminated with the acetamide **8a**, with the best result a ratio **5a**/**8a** = 64/36 in 91% yield.

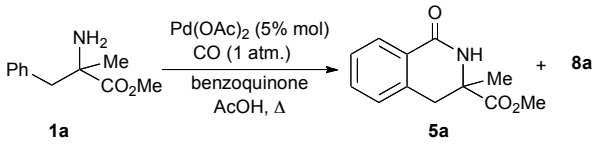


7a **8a**

Figure 1. Urea **7a** and acetamide **8a**

Since the formation of acetamide may be favoured by the Cu(II) salts which can enhance the amide bond formation,[§,10] we required an alternative oxidant. After some trials, we obtained good results using benzoquinone as the oxidant (Table 1).

Table 1. Optimization of carbonylation of **1a**



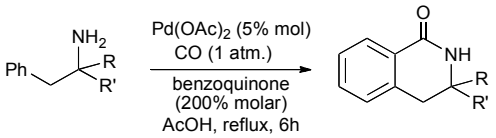
1a **5a**

Entry	t (h)	T (ºC)	Benzoquinone (% molar)	Yield (%)	**5a**/**8a**/**7a** ratio
1[a]	6	reflux	100	98	80:20:-
2	6	65	100	95	58:42:-
3	6	reflux	200	91	90:10:-
4[b]	6	reflux	100	92	70:30:-
5	6	reflux	135	98	86:14:-
6	3	reflux	200	94	84:16:-

[a]2% molar of $Pd(OAc)_2$. [b]Two-fold **1a** and benzoquinone concentration.

As shown, the best results were obtained with a $1.5 \cdot 10^{-2}$M solution of **1a** in refluxing AcOH using $Pd(OAc)_2$ (5% molar) and an amino ester/benzoquinone ratio of 1:2 molar. Under these conditions the yield was 91% and the ratio benzolactam/acetamide ratio was 90:10 (entry 3).

Table 2. Carbonylation of phenylethylamines.

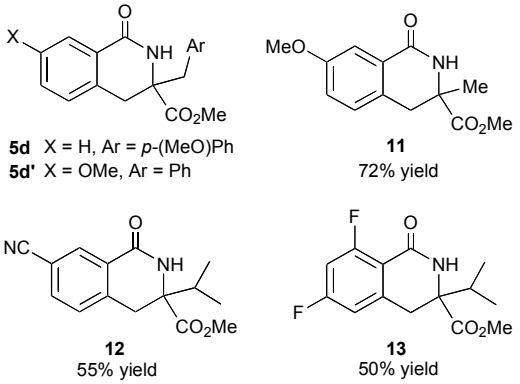


Entry	R	R'	Lactam	Yield (%)	lactam /acetamide ratio
1	CO_2Me	Propyl	**5b**	98	100:0
2	CO_2Me	Bn	**5c**	93	100:0
3	CO_2Me	*p*-MeO-Bn	**5d**/**5d'**	80[a]	100:0
4	CO_2Me	H	**5e**	91	46:54
5	CO_2Me	Allyl	–	–	[b]
6	Me	Me	**9**	89	82:18
7	CH_2OH	Bn	**10**	85	50:50[c]

[a]Mixture of regioisomers (**5d**/**5d'** = 6:4). [b]Complex mixture of compounds. [c]Lactam **10** is not acetylated on the hydroxyl group.

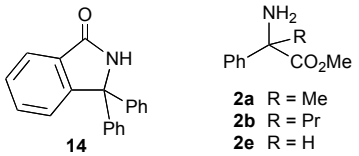
In a next step, we succesfully expanded the process to other racemic phenylethylamines. The results are summarized in Table 2.

A factor that plays a crucial role in the process is the steric hindrance due to the R and R' groups. Thus, the carbonylation of methyl phenylalaninate gave a low benzolactam/acetamide ratio (R' = H, entry 4). This ratio improved to 9:1 in compound **1a** (Table 1, entry 3, R' = Me) and no acetamides were found in the preparation of **5b–d** bearing larger R groups (Table 2, entries 1–3, R' = propyl, benzyl and *p*-methoxybenzyl respectively), showing that an increase in the steric hindrance around the amino group prevents competitive acetylation. Interestingly, the presence of the ester group ($R \neq CO_2Me$) is not essential for the success of the catalytic carbonylation (entry 6). However, the presence of a neighboring coordinating hydroxymethyl or allyl group erodes or inhibits completely the formation of benzalactam (entries 7 and 5, respectively). It should be also noted that the presence of MeO, CN or F groups on the aromatic ring (**5d'** and **11**-**13** in Scheme 2) is compatible with the formation of lactam, as shown in Scheme 2.



Scheme 2. Benzolactams substituted on the aromatic ring.

On the other hand, the reaction is highly sensitive to the size of the benzolactam formed. Although a 57% yield of 5-membered lactam **14** was obtained from triphenylmethylamine with a total selectivity, no lactams were detected when the reaction was performed with ligands **2a**, **2b** and **2e** (Figure 2). These results are in sharp contrast with those reported by Orito *et al.*[5] in the related carbonylation of secondary amines using Cu(II) as co-oxidant in wich the benzolactams of 5 members are clearly favored over the 6-membered analogues.



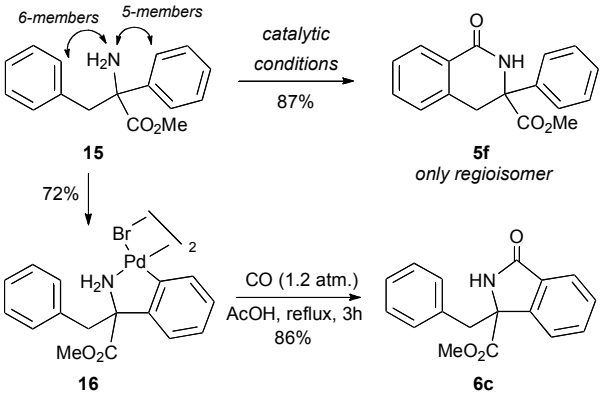
14

Figure 2. Benzolactam **14** and methyl phenylglycinates **2**

We assumed that the greater reactivity of 6-membered palladacycles could explain this result. To assess this assumption, we compared the reactivity of 5- and 6-membered cyclopalladated derivatives **3b** and **4b** (see Scheme 1) in front of CO at a moderate temperature. Thus, after 1 hour of

reaction at 50 ºC, the 6-membered benzolactam **5b** were obtained in 80% from **3b** whereas **4b** afforded only 10% of **6b**, in agreement with the catalytic results.

A further experiment was specially significant. Catalytic carbonylation of the amino ester **15**, in which both 5- and 6-membered metallacycles could be attained, gave only the lactam **5f** arising from the 6-membered metallacycle.[#] However, the stoichiometric cyclometallation of **15** gave the favored 5-membered palladacycle **16** as a major product. Carbonylation of a sample of pure **16** in refluxing AcOH in the absence of benzoquinone afforded the 5-membered lactam **6c** in 86% yield as well as a minor amount (6%) of the isomer **5f**.[¥] Thus both benzolactams sizes (6 or 5) are attainable depending on the carbonylation method (catalytic or stepwise).



Scheme 3. Catalytic and stepwise carbonylation of **15**

These experiments suggest that the 5-membered and the 6-membered palladacycles are probably in equilibrium under catalytic conditions but the latter reacts more quickly with CO, thus shifting the equilibrium to afford **5f** as the only stereoisomer.

In summary, we have demonstrated that an adequate selection of the R groups positioned on the acyclic carbon backbone of phenyethylamines and benzylamines allows an unprecedented NH_2-directed catalytic carbonylation with high selectivity and yield. In this regard, an unexpected strong bias to the 6-membered lactams over 5-membered ones has been observed in our substrates. Studies designed to expand the process to other organic derivatives of interest are currently under way.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details for the synthesis and characterization of lactams **5a–e** and **6d**. See DOI: 10.1039/b000000x/

‡ Pd(II) catalysts are readily reduced by CO, in a reaction that also affords Ac_2O, which could cause secondary reactions with primary amines. See: I. I. Moiseev, *Pure & Appl. Chem.*, 1989, **61**, 1755–1762.

¶ Mechanistic studies demonstrate that palladation of imines is a somewhat complex process in which acidolysis of Pd-C and C=N bonds and substitution on the acetato bridging positions are possible. See: M. Gomez, J. Granell and M. Martinez, *Eur. J. Inorg. Chem.*, 2000, 217–224.

§ In a blank experiment, the treatment of **1a** with $Cu(AcO)_2$ (20% molar) in refluxing AcOH for 6 h in the absence of Pd(II) salts or CO gave acetamide **8a** in 96% yield. However, the aforementioned CO-mediated reduction of $Pd(AcO)_2$ to Pd(0) and Ac_2O, which in turn can acetylate **1a**, should also be considered.

Preparation of **5f** afforded also the acetamide of **15** (18%) as a by-product.

¥ The carbonylation of **16** in the same conditions but in the presence of benzoquinone (200% molar) gave **5f** as major product indicating that benzoquinone favors the palladacycles equilibrium.

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