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One-pot amide synthesis from allyl or benzyl halides and amines by Pd-catalysed carbonylation

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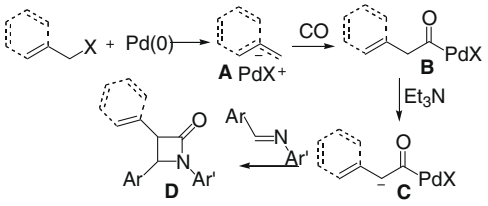
ABSTRACT

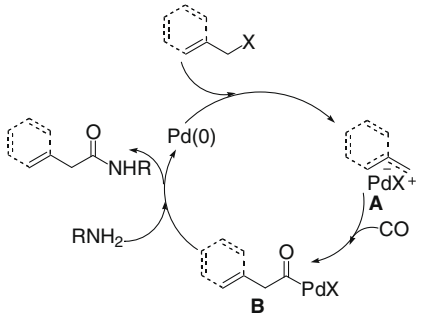
Amides can be prepared from allyl or benzyl halides and primary or secondary amines, using Pd(0) catalyst under CO pressure, in a one-pot synthesis. The reaction proceeds through the acyl palladium halide formation which undergoes an acylic nucleophilic substitution from the amine.

The amide bond is one of the most important linkages in organic chemistry and constitutes the key functional group in peptides, polymers and many natural products and pharmaceuticals.[1] A number of syntheses by which amides could be constructed are known and new methods have been developed recently.[2] Some of these methodologies were based on metal-free[3] or transition metal catalyst[4] carbonylation. Our approach was inspired by the study of palladium catalyst [2+2] cycloaddition reaction between allyl halides[5] or phosphate[6] and imines, with Et_3N under CO pressure, for the one-pot synthesis of β-lactam rings. The reaction proceeds initially with the formation of the allyl-palladium complex **A** and then with the insertion of CO generating the 3-butenyl-palladium halide (or phosphate) **B** (Scheme 1). The compound **B** is subsequently deprotonated and the carbanion **C** reacts with the imine carrying out the 2-azetidinone ring **D**.

The same pathway was noticed in the reaction between benzyl halides and imines,[7] but the [2+2] cycloaddition is slower than that observed with allyl palladium halides as a consequence of the harder formation of benzyl-Pd-complex **A**. In the second case, also the yield was lower because of the formation of *N*-Ar′-phenylacetamides. In fact, $Ar'NH_2$, produced by the imines degradation during longer reaction times, gave a nucleophilic substitution on the acyl Pd-halides generating amides. Encouraged by these results, we have treated, in the same experimental conditions used for the synthesis of 2-azetidinone ring, but without Et_3N, the benzyl chloride with the aniline instead of the imine.[8] It was noticed that the reaction proceeded with a catalytic cycle similar to that illustrated for β-lactam[5a] (Scheme 2). The reaction times were shorter than those of β-lactams formation and the *N*-Ph-acetamide was isolated as a main product with 82% of yield (Table 1, entry 1). However, as it might be expected, nucleophilic mono- and di-substitution products, **1b** and **1c**, respectively, were also formed.



Scheme 1. Synthesis of β-lactams.



Scheme 2. Catalytic cycle for amide synthesis.

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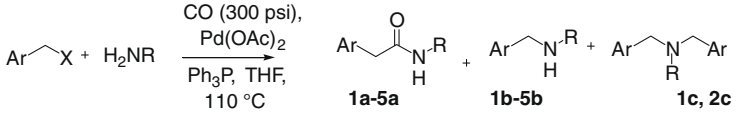
Table 1
Synthesis of amides from benzyl or pyridinyl halides and primary amines



Entry	Ar	X	R	Time (h)	Yield[a] (%)	Product distribution[b] (%)		
1	Ph	Cl	Ph	15	82	**1a** (81)[c]	**1b** (15)[c]	**1c** (4)[c]
2	Ph	Br	Ph	10	75	**1a** (70)	**1b** (23)	**1c** (7)
3	Ph	Cl	*n*Bu	15	75	**2a** (43)[c]	**2b** (27)[c]	**2c** (30)[c]
4	Ph	Br	*n*Bu	10	73	**2a** (23)	**2b** (18)	**2c** (59)
5	Ph	Br	*t*Bu	15	80	**3a** (63)[c]	**3b** (37)[c]	/
6	Ph	Cl	$PhCHCH_3$	20	60	**4a** (85)[c]	**4b** (15)	/
7	Ph	Br	$PhCHCH_3$	10	87	**4a** (46)	**4b** (54)	/
8	4Py[d]	Cl	*t*Bu	15	91	**5a** (97)	**5b** (3)[c]	/

[a] Overall yield (%) after chromatographic purification on silica gel.
[b] Product distribution determined by GC analysis.
[c] Commercially available product.
[d] Py = pyridinyl.

The reaction afforded similar results either when the benzyl chloride reacted with aliphatic amines, such as the *n*-butylamine and the 1-Ph-etanamine (Table 1, entries 3 and 6, respectively), or when 4-picolyl chloride reacted with *t*-butylamine (Table 1, entry 8). Instead, the benzyl bromide, even though reacting in a shorter reaction time, gave a smaller amount of amides and a larger amount of substitution products (Table 1, entries 2, 4, 5 and 7). According to the same general procedure, reactions between allyl chlorides and/or bromides and aliphatic and aromatic amines were conducted (Table 2).

In detail, the reactions of allyl halides with aliphatic amines were faster (2–3 h) and proceeded with 73–80% of yield, but the bromide afforded only the amine, while the chlorides generated preferably the amides (Table 2, entries 1–3). A similar trend was observed also using aniline (Table 2, entries 4 and 5).

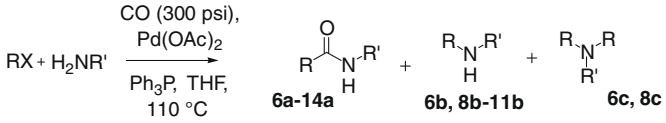
On the contrary, the lower nucleophilicity of heteroaromatic amines, such as the 2-pyridinylamine (Table 2, entries 6 and 7), the 2-thiazolylamine (Table 2, entries 8 and 9) and the 2-benzothiazolylamine (Table 2, entries 10 and 11), unfavoured the nucleophilic substitution and afforded a greater amount of amide. Moreover, branched allylchlorides afforded exclusively the amides with quantitative yields (Table 2, entries 12–14).

It was also verified that the methodology could be successfully used with secondary amines, whose results are reported in Table 3. The reaction trend was similar to that observed between primary amines and halides.

Furthermore, the isomerisation of 3-butenamides in 2-butenamides was observed. In detail, the electron-withdrawing groups (pyridinyl, thiazolyl and benzothiazolyl groups) on the amides **9a–11a** favoured the double-bond shift in conjugate position with the carbonyl unit giving the isomeric distribution shown in Scheme 3. Isomerisation was not noticed either using aliphatic amines and aniline (Table 2, products **6a–8a**) or using branched allylchloride, such as 3-methyl-1-chloro-2-butene (Table 2, products **12a–14a**). The isomerisation was also noticed for the compounds **16a** and **17a**.

In summary, we have achieved an efficient one-pot Pd-catalysed synthesis of amides, through the formation of acyl palladium species, starting from allyl or benzyl halides and different primary

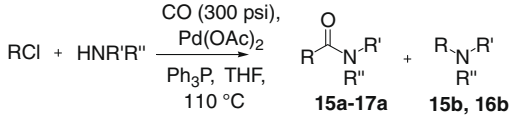
Table 2
Synthesis of amides from allyl halides and primary amines



Entry	R	X	R′[a]	Time (h)	Yield[b] (%)	Product distribution[c] (%)		
1	CH_2CHCH_2-	Cl	PhCHMe	3	75	**6a**(35)	**6b**(32)[d]	**6c**(33)[9]
2	CH_2CHCH_2-	Br	PhCHMe	3	80	/	**6b**(56)	**6c**(44)
3	CH_2CHCH_2-	Cl	*t*Bu	2	73	**7a**(100)[10]	/	/
4	CH_2CHCH_2-	Cl	Ph	15	51	**8a**(63)[11]	**8b**(37)[d]	/
5	CH_2CHCH_2-	Br	Ph	10	90	/	**8b**(60)	**8c**(40)[d]
6	CH_2CHCH_2-	Cl	2Py	15	63	**9a**(100)	/	/
7	CH_2CHCH_2-	Br	2Py	12	60	**9a**(93)[e]	**9b**(7)[d]	/
8	CH_2CHCH_2-	Cl	2Tz	12	82	**10a**(100)[e]	/	/
9	CH_2CHCH_2-	Br	2Tz	12	60	**10a**(92)	**10b**(8)[12]	/
10	CH_2CHCH_2-	Cl	2BTz	12	75	**11a**(100)[e]	/	/
11	CH_2CHCH_2-	Br	2BTz	12	55	**11a**(82)	**11b**(18)	/
12	Me_2CCHCH_2-	Cl	Ph	12	90	**12a**(100)[13]	/	/
13	Me_2CCHCH_2-	Cl	2Py	12	89	**13a**(100)	/	/
14	Me_2CCHCH_2-	Cl	2BTz	12	85	**14a**(100)	/	/

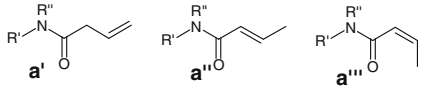
[a] Py = pyridinyl, Tz = thiazolyl, BTz = benzothiazolyl.
[b] Overall yield (%) after chromatographic purification on silica gel.
[c] Product distribution determined by GC analysis.
[d] Commercially available product.
[e] 3-Butenamide isomerises as described in Scheme 3.

Table 3
Synthesis of amides with secondary amines



Entry	R	R'	R''	Time (h)	Yield[a] (%)	Product distribution[b] (%)	
1	$PhCH_2$	Et	Et	15	41	**15a** (54)[c]	**15b** (46)[c]
2	CH_2CHCH_2	Me	Ph	15	55	**16a** (42)[d14]	**16b** (58)[c]
3	CH_2CHCH_2	Ph	Ph	15	12	**17a** (100)[d15]	/

[a] Overall yield (%) determined by GC analysis on the base of formed amides or benzyl chloride transformed.
[b] Product distribution determined by GC analysis.
[c] Commercially available product.
[d] 3-Butenamide isomerises as described in Scheme 3.



9a' (46%) **9a**'' (42%) **9a**''' (12%)
10a' (92%) **10a**'' (6%) **10a**''' (2%)
11a' (65%) **11a**'' (32%) **11a**''' (3%)

16a' (65%) **16a**'' (31%) **16a**''' (4%)
17a' (76%) **17a**'' (24%)

Scheme 3. Isomerisation of 3-butenamides (isomeric distribution determined by GC analysis).

and secondary amines. In the literature only one similar methodology was reported for the amide bond preparation, which uses allylic carbonate in DMF in the presence of Pd(II), CO and L-alanine to generate a precursor of antillatoxin.[16] Our methodology could be a novel and general access to the functionalisation of amine groups in biologically active molecules through the amide bond formation. These are on-going studies and more results will be reported in the future.

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