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# Palladium-catalyzed selective alkoxycarbonylation of α,β-unsaturated amides: a novel approach toward new ω-amido esters and N-substituted cyclic succinimides

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ABSTRACT

The alkoxycarbonylation of α,β-unsaturated amides proceeded efficiently and regioselectivity to give ω-amido esters with complete conversion in the presence of the catalyst system: $Pd(PPh_3)_2Cl_2$/MeOH/CO/$H_2O$. The reaction was successfully applied to the alkoxycarbonylation of bis-acrylamides yielding, selectively, the corresponding di-ω-amido esters. These mono and di-ω-amido esters have been used as precursors for the synthesis of N-substituted cyclic succinimides in moderate to high yields.



## 1. Introduction

N-Substituted cyclic succinimides represent a group of imide derivatives that have good antifungal, antidepressant, and antituberculosis activities.[1,2] Numerous methods have been reported for the synthesis of cyclic succinimides.[3–5] However, the availability of simple routes for their synthesis is still limited. Moreover, carbonylation methodology has never been reported as a route for the synthesis of such compounds. The alkoxycarbonylation of α,β-unsaturated amides represents a potential method for the synthesis of ω-amido esters, which can be converted into N-substituted cyclic succinimides. The synthesis of a variety of ω-amido ester precursors in high yields and regioselectivity using carbonylation methodology represents a significant advantage for the synthesis of N-substituted cyclic succinimides. The alkoxycarbonylation of unsaturated amides with alcohols normally leads to γ-amido esters and ω-amido esters. Catalytic systems developed for the alkoxycarbonylation of α,β-unsaturated amides have focused on the production of α,γ-amido esters, since these products are good precursors for the synthesis of amino acids.[6–8] To the best of our knowledge, there are no reports describing the preparation of ω-amido esters regioselectively via the alkoxycarbonylation of α,β-unsaturated amides. Moreover, the carbonylation of a double bond conjugated to carbonyl and phenyl groups in α,β-unsaturated amides has not been reported.

Considering the synthetic importance of the alkoxycarbonylation of α,β-unsaturated amides for the preparation of α,ω-amido esters, we report here the palladium-catalyzed synthesis of mono and di-α,ω-amido esters in high yields and regioselectivity. In addition, the resulting mono and di-ω-amido esters undergo elimination of an alcohol group to yield the corresponding N-substituted cyclic succinimides.

The alkoxycarbonylation of *N*-cyclohexyl-2-phenylpropenamide (**1a**, R = Ph; R′ = cyclohexyl), adopted as a model substrate, using palladium–phosphine systems was studied by varying the reaction parameters (Eq. 1) in order to optimize the reaction conditions. ω-Amido ester **4a** was the desired product, while the hydrogenation product **3a** was a by-product of the reaction. It is worth mentioning that the branched isomeric ester that normally results from carbonylation of an internal olefin was not detected in this reaction.

Since varying the solvent had a noticeable influence on both the conversion and the regioselectivity of the catalytic reactions, we carried out the alkoxycarbonylation of **1a** using $Pd(PPh_3)_2Cl_2$ as a catalyst in the presence of different solvents and the results are summarized in Table 1. No conversion of **1a** in *n*-hexane or dichloromethane was observed (Table 1, entries 1 and 2), while THF led to moderate conversion, but mainly with formation of the hydrogenation product **3a** (Table 1, entry 3). Promising regioselectivity in the formation of ω-amido ester **4a** was obtained when acetonitrile was used as the solvent (Table 1, entry 4). Our attempts to increase the conversion and the regioselectivity of the

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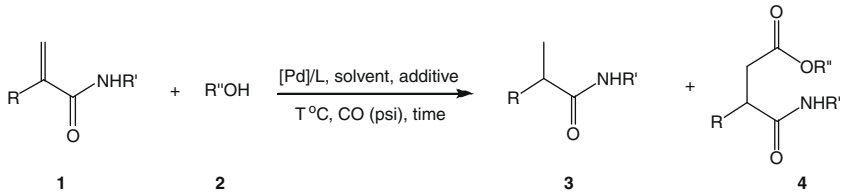
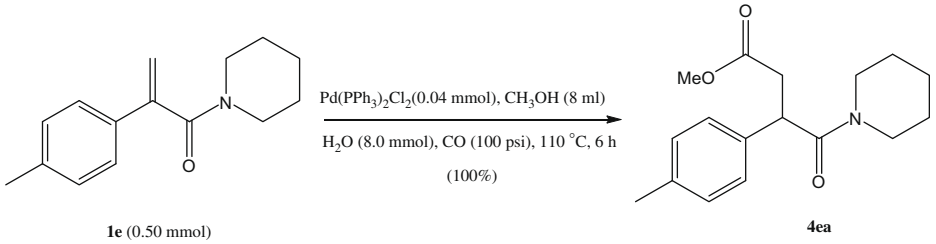



(1)

alkoxycarbonylation reaction forming **4a** were successful using neat methanol which acts as both the solvent and trapping agent (Table 1, entry 5), and also by adding an optimized amount of $H_2O$ (8 mmol) (Table 1, entry 6). The addition of water may be necessary to improve the reactivity of the α,β-unsaturated amide; perhaps a water molecule remains in proximity to the palladium throughout the catalytic cycle.[9]

In order to better understand the nature of the active palladium catalytic species involved in the alkoxycarbonylation of α,β-unsaturated amides, we studied the alkoxycarbonylation of **1a** using different palladium complexes (Table 2). A preliminary experiment with $Pd(PhCN)_2Cl_2$ as the catalyst precursor resulted in no catalytic activity in the absence of any added ligand (Table 2, entry 1). The crucial role of a phosphine ligand in enhancing the activity of the catalyst system was proved with the addition of monodentate or bidentate phosphine ligands. In these cases, good conversions and complete regioselectivity for the ω-amido ester **4a** were achieved (Table 2, entries 2–4). The good conversion obtained with $PPh_3$ as the ligand (Table 2, entry 4) encouraged us to examine the $Pd(PPh_3)_2Cl_2$ complex for the alkoxycarbonylation of **1a** (Table 2, entries 5–7), where excellent conversions and regioselectivities were obtained even in the absence of any added phosphines (Table 2, entry 6). The use of $PdCl_2/PPh_3$ as the catalyst system led to comparable activity and regioselectivity as that obtained with $Pd(PPh_3)_2Cl_2$ (Table 2, entry 8). Again, the presence of the phosphine ligand was crucial for the reaction since no catalytic activity was observed with $PdCl_2$ alone as the catalyst (Table 2, entry 9). No catalytic activity was observed in the absence of chloride; $Pd(OAc)_2$ and $Pd(PPh_3)_4$ gave no reaction even in the presence of different monophosphine ligands in the alkoxycarbonylation of **1a** (Table 2, entries 11–13).

The use of $Pd(PPh_3)_2Cl_2$ as the catalyst has been reported before for the alkoxycarbonylation of *N*-vinylphthalimide.[10] However, our proposed method showed opposite regioselectivity under milder reaction conditions.




**1e** (0.50 mmol) **4ea**

(2)

**Table 1**
Effect of solvent on the palladium-catalyzed alkoxycarbonylation of **1a** by $Pd(PPh_3)_2Cl_2$[a]

| Entry | Solvent | Conversion[b] (%) | Product distribution[c] (%) | |
|---|---|---|---|---|
| | | | **3a** | **4a** [ ][d] |
| 1 | *n*-Hexane | 0 | — | — |
| 2 | $CH_2Cl_2$ | 0 | — | — |
| 3 | THF | 64 | 93 | 7 |
| 4 | $CH_3CN$ | 40 | 38 | 62 [23] |
| 5 | $CH_3OH$ | 84 | 1 | 99 [79] |
| 6[e] | $CH_3OH$ | 100 | 0 | 100 [96] |

[a] Reaction conditions: $Pd(PPh_3)_2Cl_2$ (0.04 mmol), **1a** (0.50 mmol), $CH_3OH$ (8.0 mmol), solvent (8 ml), CO (100 psi), 110 °C, 6 h.
[b] Determined by GC.
[c] Determined by GC and $^1H$ NMR spectroscopy.
[d] Isolated yield.
[e] $H_2O$ (8 mmol) added.

Furthermore, we carried out the alkoxycarbonylation of several α,β-unsaturated amides, prepared by aminocarbonylation of terminal alkynes,[11] using various alcohols and the results are presented in Table 3. In the majority of cases, the reactions proceeded cleanly to give the desired products **4** in high yields (Table 3, entries 1–5). Surprisingly, the alkoxycarbonylation of α,β-unsaturated amide **1d** was accompanied by formation of the corresponding cyclic product **5da** (Fig. 1) in a moderate yield (Table 3, entry 6). It was interesting to observe that the activity and selectivity of the alkoxycarbonylation of α,β-unsaturated amides were not affected by the type of alcohol employed (Table 3, entries 1–3). On the other hand, the catalyst system promoted alkoxycarbonylation of the geminal bond in **1c** selectively, and not the other olefinic bond present in the molecule (Table 3, entry 5).

It is important to note that the alkoxycarbonylation reaction takes place selectively with N,N-disubstituted α,β-unsaturated amides also, for example, **1e** (Eq. 2).

The successful preparation of the ω-amido esters **4aa**–**ca** encouraged us to examine the cyclization of these compounds to afford the corresponding N-substituted cyclic succinimides **5aa**–**ca** (Eq. 3). The cyclic products were obtained in moderate to excellent yields by reacting **4aa**–**ca** with CaH as base in DMF at 50 °C. Addition of the base was essential for this cyclization step, since simple heating gave no product. DMF was the only solvent that led to good conversions compared to other polar and non-polar solvents.

Using a similar strategy, novel N-substituted bis-succinimides **9aa**,**ba** were synthesized in good yields via alkoxycarbonylation of N-substituted bis-acrylate amides **7aa**,**ba**, followed by ring closure of the resulting ω-bis-amido esters **8aa**,**8ba** (Scheme 1). The ω-bis-amido esters **8aa** and **8ba** were obtained as a 1:1 mixtures of diastereomers. To the best of our knowledge, the alkoxycarbonylation of diacrylate amides has not been reported in the literature. It is worth noting that compounds **7aa** and **7ba** have