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Convenient palladium-catalyzed carbonylative synthesis of caprolactam and butyrolactam derived phthalimides and amides by using DBU and DBN as the nitrogen source

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ABSTRACT

A novel and convenient strategy toward caprolactam and butyrolactam derived phthalimide and amide scaffolds has been fulfilled through the palladium-catalyzed carbonylative coupling in a one-pot one step manner. The nucleophilicity of DBU and DBN was applied to the carbonylation reaction for the first time and followed by hydrolysis leading to the ring opening reaction of DBU and DBN. It should be noted that the chlorobenzene worked successfully under this approach.

Introduction

Over the past several decades, palladium-catalyzed carbonylation reactions have become a powerful synthetic toolkit in the organic synthesis[1] and many attentions have been drawn to the application of carbonylation for the biological active compound synthesis.[2] Among these, the aminocarbonylation reaction has made numerous progresses.[1–3] Obviously, primary or secondary amines are more commonly used as the nucleophiles for those types of reactions. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) is usually treated as a sterically hindered, non-nucleophilic amidine type strong base.[4] Additionally, examples that serve DBU and DBN as nucleophiles have been reported as well.[5] Mayr and co-workers performed systematic studies on this topic and demonstrated that DBU and DBN have more strong nucleophilicity than DMPA in 2008.[6]

On the other hand, Phthalimide and amide derivatives have been defined as privileged scaffolds because they exhibit a wide range and applicability in the medicinal chemistry and pharmaceutical industry.[7] Classical procedures usually require relatively high temperature and long reaction time.[8] Carbonylative processes were developed for phthalimide preparation as well, which uses the corresponding amines as the reaction partners.[9] Based on our interest on manifesting useful carbonylative profiles toward bio-active motifs,[10] herein, by utilizing the advantages of nucleophilicity of DBU and DBN, we wish to report a novel palladium-catalyzed aminocarbonylation for the synthesis of caprolactam or butyrolactam derived phthalimides and amides with DBU and DBN as the coupling partners.

Discussion

At the beginning, 1,2-dibromobenzene and DBU were selected as the model reaction in the presence of 100 μL water under the commonplace conditions in our laboratory for carbonylation reaction: $Pd(OAc)_2$ (2 mol %), $BuPAd_2$ (6 mol %) under 10 bar of CO in DMAc at 100 °C. 30% of the desired product was produced (Table 1, entry 1). No product was formed if increasing the amount of water to 1 mL (Table 1, entry 2). Utilization of 1,4-dioxane as the solvent showed similar results (Table 1, entry 3). Significant progress was observed by applying $[Pd(cinnamyl)Cl]_2$ and bidentate ligand (dppp) as the catalyst system. In the presence of 50 μL of water, 61% of the wished phthalimide was formed (Table 1, entry 4). In further solvent effect testing, toluene gave the best efficiency (99% GC yield and 96% isolated yield) compared with *o*-xylene and DMAc (Table 1, entries 4–6). Control experiment proved the importance of water, only 31% of phthalimide was produced in the absence of water (Table 1, entry 8). The yield decreases dramatically when the reaction was performed under lower pressure of carbon monoxide (1 bar; <15%).

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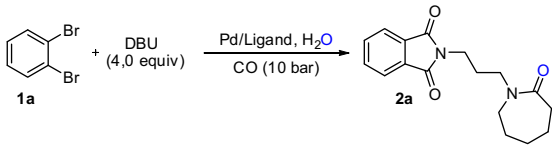
Table 1
Optimization of the reaction parameters[a]



Entry	Pd source	Ligand	Soln	H_2O (μL)	Yield[b] (%)
1	$Pd(OAc)_2$	$BuPAd_2$	DMAc	100	30[c]
2	$Pd(OAc)_2$	$BuPAd_2$	DMAc	1 mL	0[c]
3	$Pd(OAc)_2$	$BuPAd_2$	Dioxane	100	27[c]
4	$[Pd(cinnamyl)Cl]_2$	dppp	DMAc	50	61
5	$[Pd(cinnamyl)Cl]_2$	dppp	*o*-Xylene	50	10
6	$[Pd(cinnamyl)Cl]_2$	dppp	Tol.	50	**99 (96)**
7	$[Pd(cinnamyl)Cl]_2$	dppp	Tol.	100	68
8	$[Pd(cinnamyl)Cl]_2$	dppp	Tol.	0	31

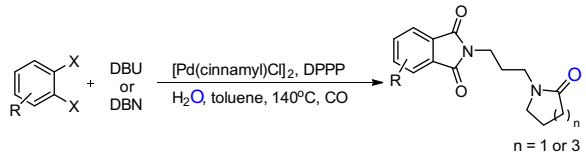
[a] Reaction conditions: 1,2-dibromobenzene **1a** (0.5 mmol, 1.0 equiv), DBU (2.0 mmol, 4.0 equiv), $Pd(OAc)_2$ (2 mol %) or $[Pd(cinnamyl)Cl]_2$ (1.5 mol %), $BuPAd_2$ (6 mol %) or dppp (3 mol %), solvent (3 mL), H_2O indicated amount, CO (10 bar), 140 °C, 16 h.
[b] GC yields with hexadecane as internal standard, isolated yields in parentheses.
[c] At 100 °C.

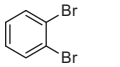
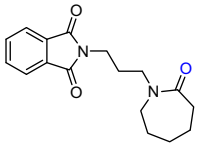
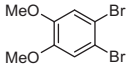
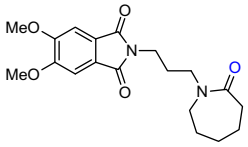
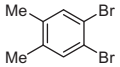
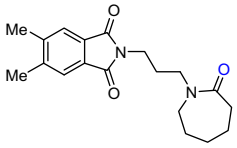
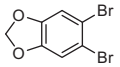
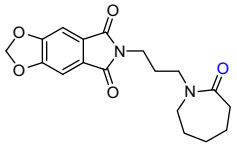
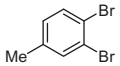
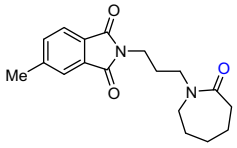
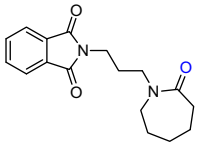
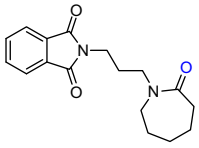
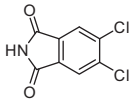
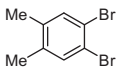
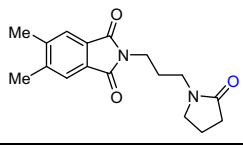
Dimethoxy or dimethyl substituted 1,2-dibromobenzene was transformed into the target molecule in good yields (Table 2, entries 2 and 3) whereas 5,6-dibromobenzo[*d*][1,3]dioxole gave the product in moderate yield (Table 2, entry 4). The 1,2-dibromo-4-methylbenzene generated the corresponding motif in moderate efficiency (Table 2, entry 5). 2,3-Dibromobenzo[*b*]thiophene, 2,3-dibromo-5-methylpyridine, 4,5-dibromo-1-methyl-1*H*-imidazole, 3,4-dibromo-1-methyl-1*H*-pyrrole-2,5-dione, and 1,2-bis(bromomethyl)benzene as examples of 1,2-dibromo compounds were tested under our conditions as well, but no desired phthalimides were detected. Compared with **1a**, 1-bromo-2-iodobenzene only gave 11% yield of the desired phthalimide while 25% was produced from 1-bromo-2-chlorobenzene (Table 2, entries 6 and 7). The reason for the differences on yields can be explained by the temperature (140 °C) induced decomposition of 1-bromo-2-iodobenzene and activation of 1-bromo-2-chlorobenzene. However, 5,6-dichloroisoindoline-1,3-dione did not run under our conditions (Table 2, entry 8). DBN as the analogue of DBU was successfully applied as well, and delivered the butyrolactam derived phthalimide in 75% yield (Table 2, entry 9). Additionally, $Mo(CO)_6$ as the alternative CO source was tested under identical conditions to replace carbon monoxide gas, but no desired product **2a** was formed.

Inspired by the result of 1-bromo-2-chlorobenzene, we envisioned that mono-bromo or even mono-chlorobenzenes might be able to be applied as the coupling partner in our system as well and providing amides as products. As shown in Table 3, different kinds of aryl bromides could be applied in this procedure and gave the corresponding amides. It should be noted that 4-acetyl chlorobenzene could also be applied as the substrate and generate the corresponding product in 34% yield (Table 3, entry 4). Unfortunately, 3-chloropyridine failed in this process.

Combining the knowledge in the literature and our own understanding,[5d,11] we proposed a plausible reaction mechanism for the synthesis of phthalimides (Scheme 1). First, the Pd(II) was reduced by ligand to generate Pd(0), then the oxidative addition of dibromobenzene **1a** to Pd(0) gave the corresponding organopalladium species **A**. Secondly, the key intermediate **B** was formed through the coordination and insertion of CO to species **A**. Then nucleophilic attack of DBU toward specie **B** took place delivering the intermediate **C** and regenerated Pd(0). Hydrolysis of intermediate **C** furnished the compound **D** which, at last, underwent intramolecular aminocarbonylation in the presence of Pd(0) generating the terminal product **2a**.

Table 2
Substrate scope for the phthalimide synthesis[a]



Entry	Substrate	Product	Yield[b]
1			96%
2			82%
3			73%
4			50%
5			46%
6			11[c] 23[c,d]
7			25[c]
8		—	0%
9			75%[e]

[a] Reaction conditions: **1** (0.5 mmol, 1.0 equiv), DBU (2.0 mmol, 4.0 equiv), $[Pd(cinnamyl)Cl_2$ (1.5 mol %), dppp (3 mol %), toluene (3 mL), H_2O (50 μL), CO (10 bar), 140 °C, 16 h.
[b] Isolated yields.
[c] GC yield.
[d] 120 °C.
[e] DBN was used in place of DBU.

In summary, a novel and interesting protocol for the synthesis of caprolactam or butyrolactam derived phthalimides and amides has been developed. The desired products were produced in low