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Pd/C-Catalyzed Reductive Carbonylation of Nitroaromatics for the Synthesis of Unsymmetrical Ureas: One-Step Synthesis of Neburon

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Abstract. A Pd/C catalyzed reductive carbonylation of nitroarenes for the synthesis of unsymmetrical ureas have been developed. Using inexpensive and stable nitroarenes as the substrates, a series of unsymmetrical ureas were produced in moderate to good yields. A range of functional groups including thioether, halides and vinyl were compatible in this reaction. As a heterogeneous catalyst, Pd/C was recycled and reused for four times without losing activity. Notably, urea-based herbicide Neburon was prepared in 64% yield under our standard conditions.

Ureas are important structure motifs in organic chemistry and have attracted considerable attention due to their wide applications in various areas such as biological,[1] pharmaceutical,[2] agrochemical,[3] material[4] and also used organocatalyst[5] (Figure 1). Owing to their importance, various methods have been developed for the synthesis of urea derivatives. Conventional procedures for the preparation of ureas were essentially based on use of highly toxic phosgene (or its analogs),[6] moisture sensitive isocyanates,[7] carbonates and carbamates,[8] which may cause serious environmental and health problems. Alternative synthetic protocols that exploit CO or CO_2 as a source of the carbonyl fragment have also been reported.[9] However, the reports usually require harsh reaction conditions (high pressures and temperatures) or toxic CO gas manipulation.

Among the related carbonylative procedures, typically aryl halides and aryl azides were used as the starting materials in the carbonylative synthesis of ureas. The availability and stability of these reagents restricted the substrate scope of these reactions. In comparison, nitroarenes are versatile, readily available and stable aromatic building blocks in organic chemistry.[10] The in-situ generation of isocyanates via reductive carbonylation of nitroaromatics have been reported. Homogeneous catalysts such as palladium and ruthenium were usually needed for these transformations (Scheme 1, a).[11] One of the main drawbacks for homogeneous catalysis is that the catalysts were usually difficult to separate. In this aspect, heterogeneous catalysts such as Pd/C turned out to be an alternative which can be separated simply by filtration. In addition, selenium[12] or sulfur[13] promoted carbonylation process for the ureas synthesis from nitroarenes have also been reported as well (Scheme 1, b). However, the high pressure of CO and excess promotor are not match with the "green chemistry" principles. Besides, in most cases, these reports usually get symmetrical diarylureas. Recently, our group have developed a series of carbonylation reaction based on formic acid as a CO surrogate.[14] $Mo(CO)_6$ was also widely used as a solid CO source.[15] Herein, we describe a Pd/C-catalyzed carbonylation of nitroarenes for the synthesis of unsymmetrical ureas with stoichiometric $Mo(CO)_6$ as a solid CO source (Scheme 1, c). The catalyst can be recycled and reused easily.

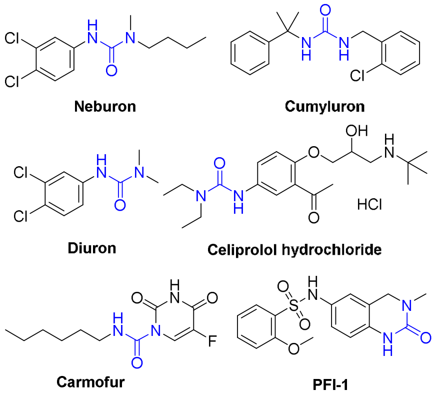
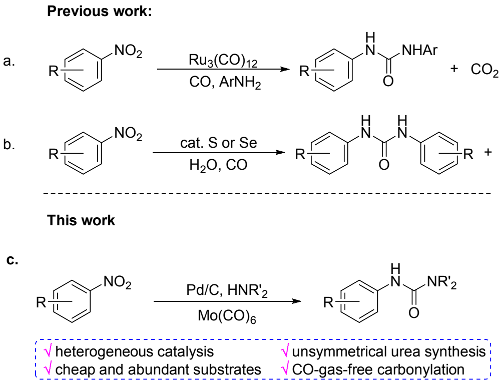


Figure 1. Selected structures of important unsymmetrical ureas.



Scheme 1. Carbonylative synthesis of ureas from nitroarenes.

We began our investigations by exploring the carbonylative reaction of 4-nitrotoluene **1d** with diethylamine **2a** as the substrates. The desired urea

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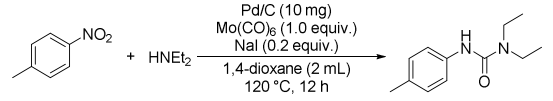
product 1,1-diethyl-3-(*p*-tolyl)urea **3da** was produced in 79% yield with Pd/C catalyst system using $Mo(CO)_6$ as a carbonyl source and NaI as additive (Table 1, entry 1). Notably, NaI additive played a crucial role in this reaction; no urea product **3da** was obtained without the addition of NaI (Table 1, entry 2). Here, the exact role of NaI in this system is not clear for the moment. One explanation is that NaI acting as a phase transfer catalyst in this system and also assistant the releasing of CO from $Mo(CO)_6$. The use of $Pd(OAc)_2$ instead of Pd/C can achieve a relatively milder yield of the product. Moreover, the monodentate ligand delivered a better yield than bidentate ligand (Table 1, entries 3-4). Other solvents, such as toluene, CH_3CN, DMF and cyclohexane, were less effective and decreased yields (Table 1, entries 5-8). It should be mentioned that reduction of nitroarene by $Mo(CO)_6$ in the presence of water was reported previously. However, no urea product was obtained when 1 equivalent of H_2O was added to the reaction system (Table 1, entry 9). Finally, reactions with other bases (DABCO, K_3PO_4 and DBU) gave either lower yields, or even no desired product (Table 1, entries 10–12).

Table 1. Reaction conditions studies for urea synthesis.[a]



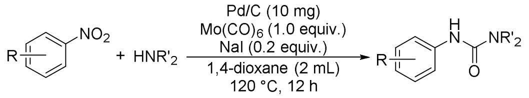
1d 2a 3da

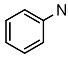
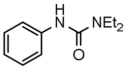
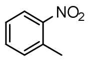
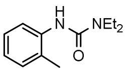
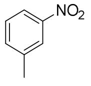
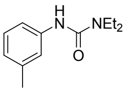
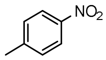
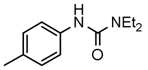
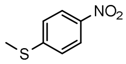
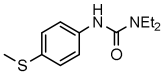
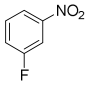
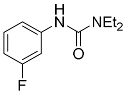
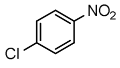
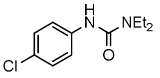
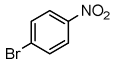
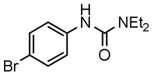
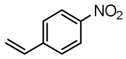
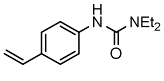
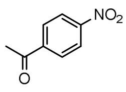
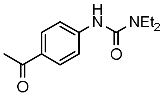
Entry	Variation from the standard conditions	Yield (%)
1	none	79
2	without NaI	trace
3[b]	$Pd(OAc)_2$, PCy_3 instead of Pd/C	70
4[c]	$Pd(OAc)_2$, Xantphos instead of Pd/C	58
5	toluene instead of 1,4-dioxane	67
6	CH_3CN instead of 1,4-dioxane	38
7	DMF instead of 1,4-dioxane	15
8	Cyclohexane instead of 1,4-dioxane	56
9	1 equiv. H_2O was added	0
10	1.5 equiv. DABCO was added	16
11	1.5 equiv. K_3PO_4 was added	trace
12	1.5 equiv. DBU was added	6

[a] Reaction conditions: **1d** (1.5 mmol), **2a** (1.0 mmol), Pd/C (10 mg), $Mo(CO)_6$ (1.0 mmol), NaI (0.2 mmol), 1,4-dioxane (2 mL), 120 °C, 12 h, isolated yield. [b] $Pd(OAc)_2$ (3 mol%), PCy_3 (6 mol%); [c] $Pd(OAc)_2$ (3 mol%), Xantphos (3 mol%).

After establishing the optimum reaction conditions, we turned our attention toward exploring various nitroarenes and amines to examine the scope of the method (Table 2). Nitrobenzene and alkyl substituted nitroarenes were successfully gave the corresponding ureas in good yields (Table 2, entries 1-4). Steric effect of the substituents affected the reaction yields significantly. For example, *meta*- and *para*-nitrotoluene gave higher yields than *ortho*-nitrotoluene (Table 1, entries 3, 4 vs entry 2). A range of functional groups including thioether, halides and vinyl were compatible in this reaction. 3-fluoro-, 4-chloro- and 4-bromo- substituted nitroarenes reacted with diethylamine and produced the corresponding ureas in 70%, 73% and 83% yields, respectively (Table 2, entries 6-8). Besides, the vinyl substituted substrate gave a corresponding product in moderate yield (Table 2, entry 9). However, when 4-nitroacetophenone was subjected to the optimized conditions, only trace amount of the desired product was detected (Table 2, entry 10). In addition to diethylamine, heterocyclic pyrrolidine and *tert*-butylamine were suitable substrates as well and provided the corresponding ureas in 58% and 69% yields, respectively (Table 2, entries 11-12). It should be noted that Neburon, a widely used herbicide in agriculture, can be prepared in 64% yield under our standard conditions (Table 2, entry 13).

Table 2. Scope of nitroarenes and alkyl amines for the synthesis of ureas.[a]



Entry	Nitroarenes	Amines	Ureas	Yield (%)
1		$HNEt_2$		56
2		$HNEt_2$		64
3		$HNEt_2$		71
4		$HNEt_2$		79
5		$HNEt_2$		65
6		$HNEt_2$		70
7		$HNEt_2$		73
8		$HNEt_2$		83
9		$HNEt_2$		46
10[b]		$HNEt_2$		trace

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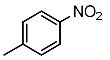
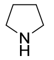
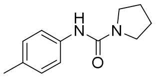
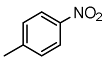
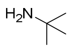
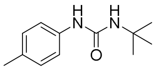
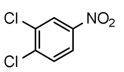
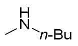
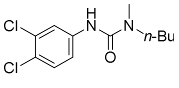
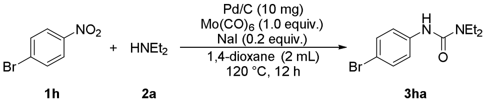
11				58
12				69
13				64

[a] Reaction conditions: Nitroarenes (1.5 mmol), amine (1.0 mmol), Pd/C (10 mg; 0.94 mol%; 10 wt.%), $Mo(CO)_6$ (1.0 mmol), NaI (0.2 mmol), 1,4-dioxane (2 mL), 120 °C, 12 h, isolated yield. [b] 16 h.

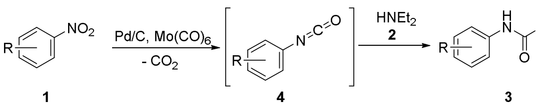
Subsequently, we examined the catalyst recycle. Pd/C can be separated simply from the reaction system by filtration and used directly for the next reaction. The catalyst can be recycled for four times without decreasing the catalytic activity (Table 3).

Table 3. Recycle of Pd/C catalyst.



Run	1	2	3	4
yield (%)	82%	81%	78%	75%

Although the detailed reaction mechanism of the reductive carbonylation of nitroarene is unclear at this stage, we believe that the reaction proceeds via the intermediacy of isocyanatobenzene **4**.[11] Thus, under the catalysis of Pd/C, nitrobenzene **1** reacted with CO, which was released in-situ from $Mo(CO)_6$, to give the isocyanatobenzene intermediate **4**. Then, nucleophilic addition of amine **2** to the isocyanatobenzene **4** produced the desired urea product **3**.



Scheme 2. Proposed reaction pathway.

In summary, ureas and its derivatives are important products with diverse biological activities. We have developed a Pd/C catalyzed reductive carbonylation of nitroarenes for the synthesis of unsymmetrical ureas. From inexpensive and stable nitroarenes, a series of unsymmetrical ureas were produced in moderate to good yields. A range of functional groups including thioether, halides and vinyl were compatible in this reaction. As a heterogeneous catalyst, Pd/C can be recycled and reused for four times without losing activity. Furthermore, urea based herbicide Neburon can be prepared under our standard conditions.

Experimental Section

An oven-dried tube, which was equipped with a magnetic stir bar, was charged with Pd/C (10 mg; 0.94 mol%; 10 wt.%), $Mo(CO)_6$ (1.0 equiv.), NaI (0.2 equiv.) and nitroarenes (1.5 equiv.) at room temperature. The tube was evacuated and backfilled with N_2 (this process was repeated 3 times). Then, a solution of diethylamine (1.0 mmol, 1.0 equiv.) in 1,4-dioxane (2 mL) was added to the reaction tube via syringe. The tube was sealed and the mixture was stirred at 120 °C for 12 h. After the reaction was completed, the reaction mixture was cooled to room temperature and filtered through a pad of Celite using excess EtOAc. The crude product was purified via flash chromatography (petroleum ether/ethyl acetate 5:1) to provide the pure product.

Acknowledgements

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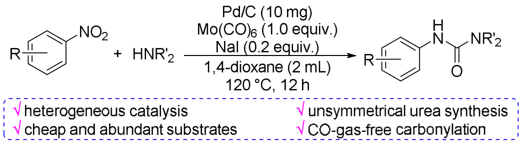

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