

# Selective formation of unsymmetric ureas by selenium-catalyzed oxidative–reductive carbonylation with CO

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## Abstract

A series of unsymmetric ureas containing substituted groups have been synthesized via selenium-catalyzed selective oxidative–reductive carbonylation of amines and nitro compounds with CO instead of phosgene in one-pot reaction. These catalytic reactions are important from both synthetic and industrial points of view, because not only the reactions can be proceeded with high selectivity of higher than 99% towards desired unsymmetric ureas, but also there exists a phase-transfer process of the selenium catalyst in the reaction, so that the after-treatment of the catalysts and products from the reaction systems can be easily separated by simple phase separation.

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**Keywords:** CO; Selective; Oxidative–reductive carbonylation; Phase transfer catalysis; Selenium; Unsymmetric ureas

## 1. Introduction

Symmetric, unsymmetric, substituted ureas that contain the peptide bond (–CONH–), many of which possess biological activities, are widely used as herbicides, agrochemicals and pharmaceuticals [1,2]. The methods for their industrial synthesis have to use phosgene as one of the reagents, but phosgene is highly toxic and produces a lot of corrosive contaminants [3,4]. In recent years, attention has been paid to a very promising non-phosgene process for the synthesis of various unsymmetric ureas, namely, the reductive carbonylation of nitro-compounds or the

oxidative carbonylation of anilines catalyzed by noble metals, including rhodium, ruthenium and palladium [5–8]. However, oxidative carbonylation of amines or reductive carbonylation of nitro-compounds by selenium catalysts instead of noble metals has been reported to give symmetric ureas [9,10].

Recently, our studies have been extended to synthesis of unsymmetric ureas by using of selenium catalyzed system. Remarkably high chemoselectivity was simultaneously observed for selective oxidative–reductive carbonization of nitro-compounds and anilines as reagents with CO [11–15].

In this work, we report a series of unsymmetric ureas synthesized in one-pot reaction by combining selenium-catalyzed oxidative carbonylation of anilines with reductive carbonylation of nitro-compounds under relatively mild conditions used. In the reaction, the nitro-compound acts as a reagent as well as an oxidant,

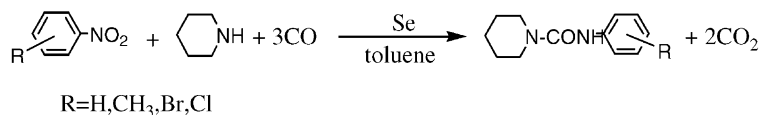
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which plays an important role in the formation of a catalytic cycle. The products can thus be easily obtained by simple phase separation. Hence, a simple, effective and new method, in which the oxidative carbonylation of amines is combined with reductive carbonylation of nitro-compounds and the selenium is used as catalyst for the synthesis of unsymmetric ureas, has been developed.

## 2. Experimental

The carbonylation reaction was carried out in a 70 ml stainless steel autoclave, which was placed in a thermostatic oil bath. The stirring rates were kept constant for all the experiments. Reaction materials including aromatic nitro-compound, amine, organic solvent, catalyst Se and co-catalyst Et<sub>3</sub>N were introduced into the autoclave. The reactor was sealed, flushed three times with 2.0 MPa of CO, and checked for leaks. Then the autoclave was pressurized with CO, and placed in the oil bath preheated to reaction temperature.

The purity of the products was determined by a Waters HPLC, with MeOH-H<sub>2</sub>O mixed solvent as eluent. Selectivities of desired unsymmetric ureas are higher



than 99%. Melting points were determined on a Taike X-4 apparatus (Beijing, China) and were uncorrected. <sup>13</sup>C and <sup>1</sup>H NMR spectra were recorded on a Bruker DRX 400 spectrometer with CDCl<sub>3</sub> as solvent and Me<sub>4</sub>Si as internal standard.

## 3. Results and discussion

### 3.1. Selective oxidative–reductive carbonylation of amines and aromatic nitro-compounds

Selenium-catalyzed reductive carbonylation of aromatic nitro-compounds, with piperidine as coreagents and forming unsymmetric phenylureas, has been conducted in Table 1 Eq. (1). Oxidative–reductive

Table 1  
Carbonylation of aromatic nitro-compounds with piperidine as coreagent

Substrate	Product	Yield (%)
		80.0
		64.0
		55.3
		40.6
		24.5
		–

Reaction conditions: substrate = 10 mmol; ArNO<sub>2</sub> = 10 mmol; Se = 0.5 mmol; Et<sub>3</sub>N = 10 mmol; CO = 3.0 MPa; PhMe = 10 g; 150–160 °C; 1.5 h.

carbonylation of aromatic nitro-compounds except 2-ClC<sub>6</sub>H<sub>4</sub>NO<sub>2</sub>, with secondary amines as coreagents give simple unsymmetric ureas. The selectivity of unsymmetric urea is about 99.1%.

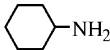
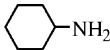

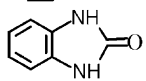
When the nitro-compounds are fatty nitro-compounds, oxidative carbonylation of amines can only give symmetric ureas containing some amine group, as shown in Table 2. The yields of symmetric ureas increase in the presence of fatty nitro-compounds.

### 3.2. Selective oxidative–reductive carbonylation of heterocyclic amines and nitro compounds

Selenium catalyzed selective oxidative–reductive carbonylation of heterocyclic amines, such as 2-aminopyridine, 3-aminopyridine or 4-aminopyridine and nitro compound to form simple unsymmetric heterocycle urea, with Et<sub>3</sub>N as cocatalysts, has been conducted Eq. (2). The yields are from moderate to good and the selectivity of the desired urea is 70–80% (Table 3). Although, the heterocyclic amines are pri-

Table 2

The results of the carbonylation of MeNO<sub>2</sub> and amines with Co<sup>a</sup>

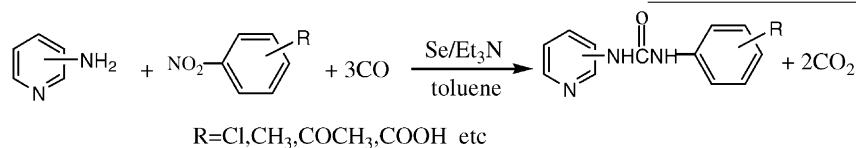
Amine	Product	Yield (%)	
		Without MeNO <sub>2</sub>	With MeNO <sub>2</sub>
<i>n</i> -BuNH <sub>2</sub>	( <i>n</i> -BuNH) <sub>2</sub> CO	33.5	56.1
<i>i</i> -PrNH <sub>2</sub>	( <i>i</i> -PrNH) <sub>2</sub> CO	55.4	91.2
PhCH <sub>2</sub> NH <sub>2</sub> <sup>b</sup>	(PhCH <sub>2</sub> NH) <sub>2</sub> CO	30.0	64.0
	(  -NH) <sub>2</sub> CO	55.8	90.0
		40.2	76.1
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>13</sub> NH <sub>2</sub>	(CH <sub>3</sub> (CH <sub>2</sub> ) <sub>13</sub> NH) <sub>2</sub> CO	82.7	90.9
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>17</sub> NH <sub>2</sub>	(CH <sub>3</sub> (CH <sub>2</sub> ) <sub>17</sub> NH) <sub>2</sub> CO	83.7	92.1

<sup>a</sup> Reaction conditions: substrate = 0.02 mol; Se = 0.5 mmol; MePh = 10 g; CO = 2.0 MPa; 140 °C; 2 h.<sup>b</sup> Reaction conditions: 0.1 mmol Se was used.<sup>c</sup> Reaction conditions: 0.01 mol Et<sub>3</sub>N was used.

mary amines, the selectivity of the desired urea is not low [11]. When the nitro-compounds are fatty nitro-compounds, unsymmetric heterocycle urea is not obtained.

### 3.4. Phase-transfer function of selenium-catalyzed system

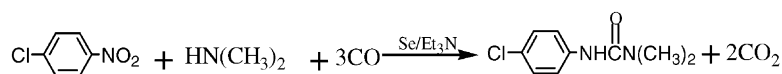
It is interesting that the selenium catalyst and the organic layer can be recycled for use, after the



(2)

### 3.3. Selective formation of monuron


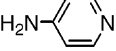
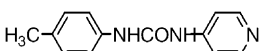
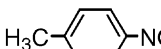
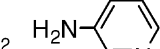
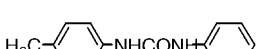
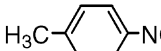
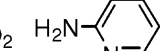
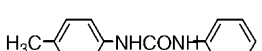

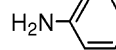

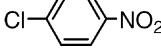
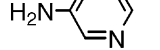

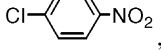
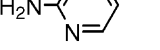

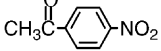
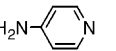
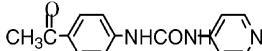
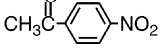
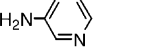
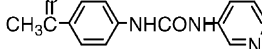
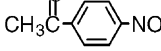
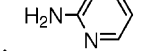
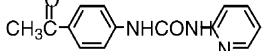
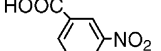
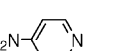
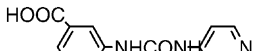
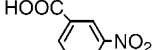
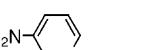
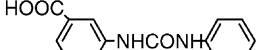
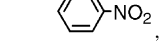
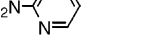
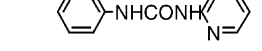

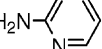
The effect of various reaction conditions on the selective formation of the monuron that is the herbicide by selenium-catalyzed oxidative–reductive carbonylation of *p*-ClC<sub>6</sub>H<sub>4</sub>NO<sub>2</sub> and HN(CH<sub>3</sub>)<sub>2</sub> (33%)/H<sub>2</sub>O (67%) are shown Eq. (3) in Table 4. It can be seen that the carbonylation yield increases with the increase of the reaction temperature (100–130 °C), the CO pressure (1–3 MPa) and the reaction time (1–4 h). From the results of entries 3–5 it is found that the yield of selective oxidative–reductive carbonylation decreases as temperature increases to above 135 °C, because monuron is hydrolysed. Under the condition of 135 °C, *P*<sub>CO</sub> = 3.0 MPa and 4 h, the yield of monuron was 54.5% (according to *p*-ClC<sub>6</sub>H<sub>4</sub>NO<sub>2</sub>). The selectivity of monuron is 99.7%.



(3)

monuron was separated. Nearly no loss in the reactivity has been detected (entries 6–9 in Table 4). Before the reaction, the selenium catalyst was in the solid state in this selenium-catalyzed system, which is different in phase with the reagents. During the reaction process, selenium reacts with carbon monoxide to form SeCO, which can then dissolve in the solvent to form a homogeneous catalytic system. After the reaction, the solid selenium catalyst is reappeared and can be separated from the solution of the product. Therefore, an special oxidant is not necessary to be added in the reaction system, and the intermediate hydroselenium can be oxidized to selenium. The nitro-compound, which is one of the reagents, can impel the recycling of the catalyst

Table 3  
Carbonylation of different substituted nitrobenzene with aminopyridine

Substrate	Product	Yield (%)
 , 		50.6
 , 		59.7
 , 		53.8
 , 		45.4
 , 		42.1
 , 		33.5
 , 		90.7
 , 		84.7
 , 		56.1
 , 		54.7
 , 		56.7
 , 		48.7
 , 	–	–

Reaction conditions: substrate = 10 mmol; Se = 0.5 mmol; Et<sub>3</sub>N = 10 mmol; PhMe = 10 g; CO = 3.0 MPa; 130 °C; 4 h.

Table 4

Selective redox carbonylation of *p*-ClC<sub>6</sub>H<sub>4</sub>NO<sub>2</sub> and HN(CH<sub>3</sub>)<sub>2</sub> catalyzed by selenium<sup>a</sup>

Entry	Cycle <sup>b</sup>	Temperature (°C)	<i>P</i> <sub>co</sub> (MPa)	Time (h)	Yield (%)	Selectivity (%)
1	0	100	3	4	3.4	99.7
2	0	125	3	4	21.8	99.7
3	0	135	3	4	54.5	99.7
4	0	145	3	4	45.9	99.7
5	0	150	3	4	36.9	99.7
6	1	135	3	4	67.9	99.6
7	2	135	3	4	79.9	99.6
8	3	135	3	4	112.7	99.5
9	4	135	3	4	104.4	99.5
10	0	135	1	4	32.6	99.7
11	0	135	2	4	43.6	99.7
12	0	135	4	4	54.7	99.7
13	0	135	3	8	44.3	99.8
14	0	135	3	6	47.9	99.8
15	0	135	3	2	29.2	99.8
16	0	135	3	1	17.4	99.8

<sup>a</sup> Reaction conditions: Se = 0.5 mmol, *p*-ClC<sub>6</sub>H<sub>4</sub>NO<sub>2</sub> = 10 mmol, HN(CH<sub>3</sub>)<sub>2</sub> (33%)/H<sub>2</sub>O (67%) (20 mmol), (CH<sub>3</sub>)<sub>2</sub>CO (10 ml), Et<sub>3</sub>N (1.4 ml).

<sup>b</sup> Number of catalyst and organic layer recycles.

continuously. The catalyst can also be separated from the product by simple phase separation. In the reaction, the selenium-catalyzed system has a function of phase-transfer catalysis and enable toxic selenium catalysts to be easily recovered and reused. Thus, there exists a phase transfer phenomenon of catalyst in this catalytic reaction system. That is, the reaction system changes from heterogeneous to homogeneous and recycles to the heterogeneous separation.

## Acknowledgements

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