

# *N*-Arylamides from Selenium-Catalyzed Reactions of Nitroaromatics and Amides in the Presence of Carbon Monoxide and Mixed Organic Bases

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**Abstract:** *N*-Arylamides were exclusively obtained in moderate to good yields from selenium-catalyzed reactions of nitroaromatics with amides in the presence of CO and mixed organic bases Et<sub>3</sub>N and DBU.

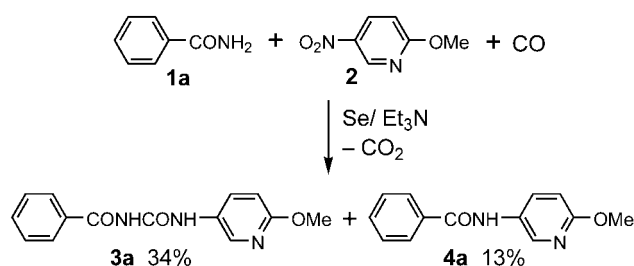
**Keywords:** acylation; carbon monoxide; *N*-arylamides; nitroaromatics; selenium

Acylation of aromatic compounds is an important process in synthetic chemistry. Friedel–Crafts reaction and other less common methods for acylation have been developed.<sup>[1–4]</sup> For instance, Suzuki<sup>[1]</sup> developed a new acylation reaction using imidazolidenylcarbene as the catalyst and Seyferth<sup>[2]</sup> has shown the acylation of electrophiles with acyllithiums to produce  $\alpha$ -hydroxy ketones and  $\alpha$ -diketones. *N*-Arylamides have been widely used in self-assembly processes to control dimensional propagation<sup>[5]</sup> and construction of model systems for polypeptides and proteins.<sup>[6]</sup> *N*-Arylamides can also be prepared by *N*-acylation of aromatic amines with phosgene. We have recently reported the selenium-catalyzed reductive carbonylation of nitroaromatics to afford unsymmetrical ureas.<sup>[7]</sup> Both Sonoda's<sup>[8]</sup> and our laboratories<sup>[9]</sup> reported that nitroaromatics can be transformed into anilines with CO and water using selenium as the catalyst. Herein we report the novel selenium-catalyzed synthesis of *N*-arylamides from formal reductive *N*-acylation of nitroaromatics with amides in the presence of CO and organic bases Et<sub>3</sub>N and DBU.

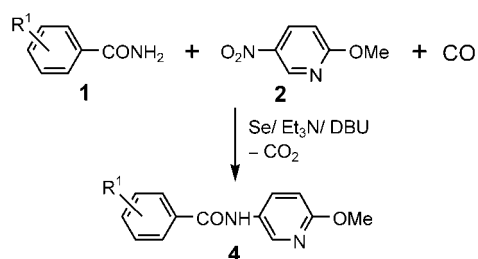
Our original intention was to prepare *N*-pyridyl-*N'*-benzoylureas by coupling reductive carbonylation of nitropyridine and oxidative carbonylation of benzamide in a one-pot reaction as shown in Scheme 1. Thus treatment of benzamide (**1a**) and 2-methoxy-5-nitropyridine (**2**) with carbon monoxide in the presence of a catalytic amount of selenium and the co-catalyst triethylamine in toluene at 160 °C afforded *N*-(6-methoxy-3-pyridyl)-*N'*-benzoylurea (**3a**) together with *N*-(6-methoxy-3-pyri-

dyl)benzamide (**4a**) in 34% and 13% yields, respectively. When other substituted benzamides were applied to this catalytic reaction system, reductive carbonylation and acylation of the nitro groups took place competitively to give a mixture of compounds of types **3a** and **4a** with varying ratios of **3** to **4**. On using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) instead of Et<sub>3</sub>N as the co-catalyst, **4a** was exclusively formed in 62% yield from the reaction of **1a** and **2** under the same conditions. Surprisingly, **4a** was obtained in a higher yield, i.e., 76% (Table 1, entry 1) by use of a combination of Et<sub>3</sub>N and DBU as the co-catalyst.

The formation of *N*-pyridylbenzamides has never been reported by means of non-metallic selenium-catalyzed reactions of benzamides and nitropyridines.<sup>[7–11]</sup> It was also found that benzamide derivatives and substituted nitropyridines underwent the same type of reactions, exclusively forming the corresponding *N*-pyridylbenzamides (Scheme 2 and Table 1). It is noteworthy that *N*-pyridyl-*N'*-benzoylureas of type **3** were not detected by HPLC-MS analysis. As shown in Table 1 substituted benzamides **1** readily reacted with nitropyridine **2** in the presence of selenium, Et<sub>3</sub>N/DBU and carbon monoxide under relatively mild conditions. Yields of **4b–e** were good and higher than those of **4a**, **4f** and **4g** (Table 1), demonstrating that the reactions are electronically influenced by substituents on the aromatic rings (Scheme 2). The presence of an intermolecular hydrogen bond in 2-chlorobenzamide and the electron-with-



Scheme 1.

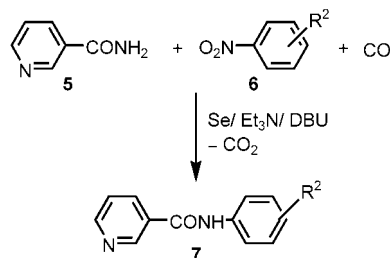


Scheme 2.

**Table 1.** Formation of **4** from the reaction of substituted benzamides and 2-methoxy-5-nitropyridine.

| Entry | R <sup>1</sup> | Product   | Mp [°C] (Ref.)                         | Isolated Yield [%] |
|-------|----------------|-----------|----------------------------------------|--------------------|
| 1     | H              | <b>4a</b> | 136–138<br>(139–140 <sup>[12a]</sup> ) | 76                 |
| 2     | 2-Me           | <b>4b</b> | 119–120                                | 80                 |
| 3     | 3-Me           | <b>4c</b> | 102–103                                | 81                 |
| 4     | 4-Me           | <b>4d</b> | 168–169                                | 84                 |
| 5     | 3,5-di-Me      | <b>4e</b> | 134–136                                | 87                 |
| 6     | 2-Cl           | <b>4f</b> | 112–114                                | 49                 |
| 7     | 4-Cl           | <b>4g</b> | 196                                    | 68                 |

Reaction conditions: Se, 0.5 mmol; substituted benzamide, 10 mmol; 2-methoxy-5-nitropyridine, 10 mmol; Et<sub>3</sub>N, 20 mmol; DBU, 10 mmol; CO, 3.0 MPa; toluene, 10 mL; 160 °C, 4.0 h.



Scheme 3.

**Table 2.** Formation of **7** from the reaction of nicotinamide and substituted nitrobenzenes.

| Entry | R <sup>2</sup> | Product   | Mp [°C] (ref.)                      | Isolated Yield [%] |
|-------|----------------|-----------|-------------------------------------|--------------------|
| 1     | H              | <b>7a</b> | 116–119 (118–119 <sup>[12b]</sup> ) | 62                 |
| 2     | 2-Me           | <b>7b</b> | 103–105 (105 <sup>[12c]</sup> )     | 83                 |
| 3     | 3-Me           | <b>7c</b> | 109–112                             | 55                 |
| 4     | 4-Me           | <b>7d</b> | 145–147                             | 57                 |
| 5     | 4-Et           | <b>7e</b> | 124–126                             | 60                 |
| 6     | 4-OEt          | <b>7f</b> | 173–176 (175–176 <sup>[12d]</sup> ) | 56                 |
| 7     | 4-OPh          | <b>7g</b> | 147–149 (149–150 <sup>[12e]</sup> ) | 63                 |
| 8     | 3-Cl           | <b>7h</b> | 140–143                             | 41                 |
| 9     | 2-Me-3-Cl      | <b>7i</b> | 141–142                             | 85                 |
| 10    | 3-Br           | <b>7j</b> | 136–138                             | 46                 |

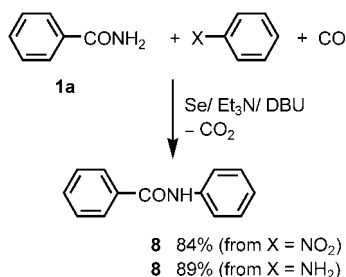
Reaction conditions: Se, 0.5 mmol; nicotinamide, 10 mmol; substituted nitrobenzene, 10 mmol; Et<sub>3</sub>N, 20 mmol; DBU, 10 mmol; CO, 3.0 MPa; toluene, 10 mL; 160 °C, 4.0 h.

drawing property of chloride led to a poor yield of **4f** (Table 1, entry 6).

Nicotinamide **5** and substituted nitrobenzenes **6** also underwent the same type of reactions to give C-pyridyl-N-arylamides **7** under the same reaction conditions (Scheme 3 and Table 2). 2-Methylnitrobenzenes gave the highest yields (83–85%) of the products (Table 2, entries 2 and 9). In other cases, the electronic properties of the substituent on the phenyl ring affect formation of **7**.

It is worthy of note that both reactions described in Scheme 4 afforded C-pyridyl-N-phenylbenzamide **8** in good yields (84% and 89%, respectively) under the reaction conditions stated in Tables 1 and 2. Reaction of benzamide (**1a**) and aniline to form **8** indicates that nitrobenzene may also be reduced to aniline,<sup>[8,9]</sup> followed by acylation with benzamide (**1a**) in the presence of CO. The reaction mechanisms are proposed in Figure 1. Nitrene (**A**) is proposed to be formed from ArNO<sub>2</sub> with *in situ* generated species SeCO and further reacts with SeCO to produce isocyanate (**B**).<sup>[7,13]</sup>

Addition of benzamide to **B** affords ArNHCONHCOAr' (**C**). Compound **C** is then decomposed to the product ArNHCOAr' and species HN=C=O which may be bound to selenium in the form of [HN=C=O]Se. =O]Se. Elemental selenium was recovered from the mixture after the reaction had been quenched in air by addition of aqueous HCl, and also formamide (HCONH<sub>2</sub>) from the hydrolysis of HN=C=O was detected by GC-MS analysis. Without DBU compound **C** could be collected in considerable yields by use of Et<sub>3</sub>N as the co-catalyst (Scheme 1) and no **C** could be obtained when DBU was used, which indicates that the strong organic base DBU prompts the complete decomposition of **C** into the product under the reaction conditions. The alternative mechanism (**b**) is partially attributed to the formation of product ArNHCOAr' by involvement of water from the reagents. Because all the solvents and materials were used as supplied and, especially, a considerable amount of water is present in Et<sub>3</sub>N



Scheme 4.

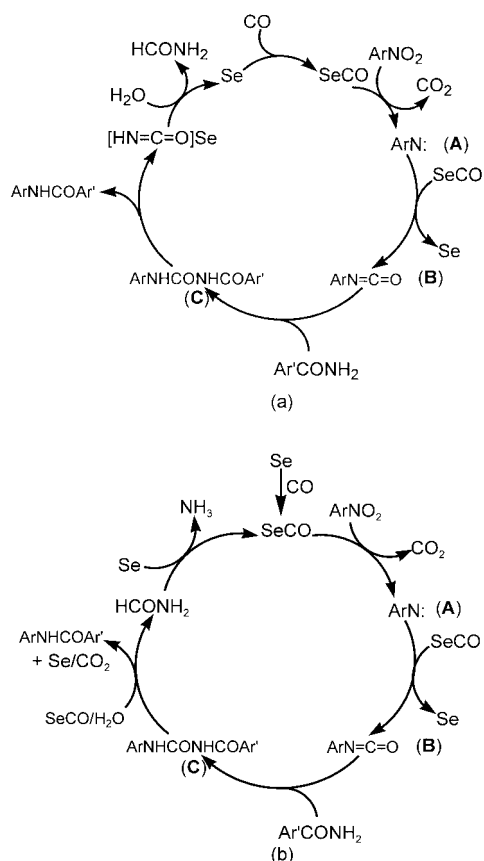


Figure 1. Proposed reaction mechanisms.

and DBU, a hydrogen source from water can be rationalized to promote formation of the product. Keeping this in mind, 1.0 equiv. of water was applied in the reaction of **1a** and nitrobenzene, **8** was obtained in 39% yield, demonstrating that water can be involved in formation of the product.

In conclusion, we have demonstrated the first examples of formal reductive acylation of nitroaromatics with amides in the presence of selenium, CO, Et<sub>3</sub>N and DBU.

## Experimental Section

### Typical Procedure for N-(6-Methoxy-3-pyridyl)benzamide (**4a**)

Selenium (39.5 mg, 0.5 mmol), benzamide (1.22 g, 10 mmol), 2-methoxy-5-nitropyridine (1.54 g, 10 mmol), triethylamine (2.02 g, 20 mmol), DBU (1.52 g, 10 mmol) and toluene (10 mL) were successively loaded in a 100-mL stainless-steel autoclave. The reactor was sealed, flushed with 1.0 MPa of carbon monoxide for three times, pressurized with 3.0 MPa carbon monoxide, and then placed in an oil bath preheated to 160 °C. After the reaction was complete, the apparatus was cooled to ambient temperature, and the remaining carbon monoxide was evacuated. The reaction mixture was poured into aqueous 1 N HCl (50 mL), and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 50 mL). The organic phase was dried over MgSO<sub>4</sub>, filtered and all the volatiles were evaporated under reduced pressure. The resultant crude product was purified by flash column chromatography on silica gel (v/v, hexane/EtOAc = 5 : 1) to afford **4a** as colorless needles; yield: 1.73 g (76%); mp 136–138 °C (Lit.: 139–140 °C<sup>[12a]</sup>); IR (KBr):  $\nu = 3308$  ( $\nu_{\text{N-H}}$ ), 1640 ( $\nu_{\text{C=O}}$ ), 1578, 1510, 1485, 1450 ( $\nu_{\text{C=C, C=N}}$ ), 1379  $\text{cm}^{-1}$  ( $\nu_{\text{CH}_3}$ ); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 23 °C):  $\delta = 3.90$  (s, 3H, OCH<sub>3</sub>), 6.71 (d,  $J = 8.8$  Hz, 1H), 7.42 (t,  $J = 7.6$  Hz, 2H), 7.51 (t,  $J = 7.2$  Hz, 1H), 7.84 (d,  $J = 7.6$  Hz, 2H), 7.95 (dd,  $J = 8.8, 2.8$  Hz, 1H), 8.07 (s, 1H, NH), 8.25 (s, 1H); <sup>13</sup>C{<sup>1</sup>H} NMR (400 MHz, CDCl<sub>3</sub>, 23 °C):  $\delta = 53.75, 110.71, 127.23, 128.80, 131.99, 132.94, 134.50, 139.45, 161.38, 166.24$ .

Other products were identified by NMR and HPLC-MS measurements and/or comparison with the authentic samples.

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