Selenium-Catalyzed Carbonylation of Nitroarenes to Symmetrical 1,3-Diarylureas under Atmospheric Pressure

Xiaofang Wang, Shiwei Lu,* Zhengkun Yu*

National Engineering Research Center for Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences,
457 Zhongshan Road, Dalian, Liaoning 116023, P. R. China
Fax: (+86)-411-8437-9227, e-mail: zkyu@dicp.ac.cn

Received: December 30, 2003; Accepted: May 13, 2004

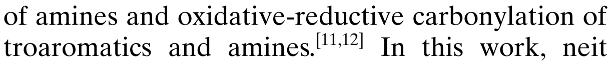
Abstract: Selenium-catalyzed carbonylation of nitrobenzene and substituted nitroarenes with CO under atmospheric pressure afforded symmetrical 1,3-diarylureas in yields up to 94%. A mechanism has been proposed to demonstrate the formation of symmetrical ureas.

Keywords: carbonylation; 1,3-diarylureas; nitroarenes; selenium catalysis

Substituted ureas have attracted considerable attention due to their wide range of applications, e.g., for use as antidiabetic and tranquillizing drugs, antioxidants in gasoline, corrosion inhibitors and herbicides.[1] Furthermore, 1,3-disubstituted ureas are important intermediates in the production of carbamates from which some important agrochemicals can be synthesized. Conventional methods to prepare ureas have been essentially based on use of phosgene or isocyanates,[2] phosgene substitutes,[3] carbonates and carbamates,[4] or carboxylic acid derivatives.[5] Recently, alternative synthetic procedures for ureas have been developed involving the use of carbonyl derivatives such as CO and CO_2.[6] Carbonylation of nitroarenes has been an attractive area with high academic and industrial interest. Transition metal-catalyzed carbonylation of nitroarenes with CO and water can afford ureas as the major products and CO_2 as the co-product,[7] avoiding the danger of mixing CO with O_2 as in the oxidative carbonylation of amines.[8] However, carbonylation reactions of nitroarenes to ureas with expensive transition metals such as Ru or Rh are usually carried out under very harsh conditions, i.e., high pressure of carbon monoxide and high temperature.[7] The work from our laboratories[9] and the Sonoda group[10] has demonstrated that the selenium-catalyzed carbonylation of nitroarenes with CO in the presence of water produces anilines in high yields.

In the course of our ongoing investigations on the selenium-catalyzed carbonylation of nitroarenes[11] we have recently discovered that symmetrical 1,3-diphenylurea (DPU) or 1,3-diarylureas could be obtained as the major products from the carbonylation of nitrobenzene or substituted nitroarenes using a concentrated reaction mixture containing a smaller amount of water than that used in the literature.[9,10] Herein, we report the synthesis of symmetrical ureas, i.e., 1,3-diphenylurea and substituted 1,3-diarylureas from the selenium-catalyzed carbonylation of nitroarenes with bubbling CO in the presence of water under atmospheric pressure for the first time.[8d,9–12]

The carbonylation of nitroarenes was carried out with bubbling CO and water by using non-metallic selenium as the catalyst in *N,N*-dimethylformamide (DMF) at 95 °C under atmospheric pressure [Eqs. (1) and (2)]. The representative results are listed in Tables 1 and 2. The use of a polar aprotic solvent such as DMF is essential for the reaction. No reaction or low conversion of the nitroaromatic compound was observed in an apolar solvent or other polar aprotic solvents such as toluene, THF, pyridine, or DMSO, although toluene is usually used as the solvent for selenium-catalyzed oxidative-reductive carbonylations of nitroarenes and amines.[11,12]



(1)

The base plays an important role in the reactions (Tables 1 and 2). The reaction proceeded very slowly in the absence of a base (Table 1, Run 1). Organic bases such as NEt_3 and DBU have been known as the co-catalysts in the selenium-catalyzed oxidative carbonylation of amines and oxidative-reductive carbonylation of nitroaromatics and amines.[11,12] In this work, neither NEt_3 nor DBU demonstrated any efficient co-catalytic activity (Table 1, Runs 2 and 3), presumably partially due to their high volatility and quick evaporation under the reaction conditions, resulting in low conversion (15%) of nitrobenzene over a period of 9 hours for NEt_3 (Table 1, Run 2) and a moderate conversion (58%) of nitrobenzene with a low yield of DPU (20%) for DBU (Table 1, Run 3). NaOAc showed a much better co-catalytic activity than NEt_3 and DBU for the carbonylation of nitrobenzene (Table 1, Run 4). Moderate

DOI: 10.1002/adsc.200303244

Table 1. Carbonylation of nitrobenzene to 1,3-diphenylurea (DPU).

Run	Base (mmol)	Time [h]	Conversion [%][a]	Yield [%][b]
1	none	12	21	16
2	Et_3N (5)	9	15	9
3	DBU (3)	12	58	20
4	NaOAc (5)	12	61	55
5	KOH (1)	12	60	53
6	KOH (2)	12	100	88
7	KOH (3)	11	100	89
8	KOH (5)	11	100	91
9	KOH (8)	12	100	86
10[c]	KOH (5)	10	<1	–

Reaction conditions: nitrobenzene, 1.847 g (15 mmol); bubbling CO, 20 mL/min; H_2O, 0.5 mL (27.7 mmol); selenium, 0.030 g (0.38 mmol); DMF, 10 mL; 95 °C.

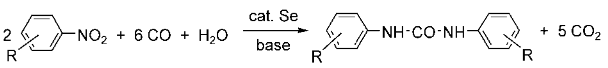
[a] Determined by HPLC and/or TLC.

[b] Yield of isolated product.

[c] Without selenium.

conversion of nitrobenzene (60%) and yield of DPU (53%) were achieved in the presence of potassium hydroxide (1.0 equiv.) (Table 1, Run 5). Surprisingly, increasing the molar ratio of KOH to nitrobenzene led to a complete conversion of nitrobenzene and formation of DPU in 86–91% yields (Table 1, Runs 6–9). Very small amounts of aniline and certain amounts of unknown materials were formed as the minor products ($<10\%$). The molar ratios of KOH to nitrobenzene ($\geq 2.0/15.0$) only slightly affected the yields of isolated DPU. 1,3-Diphenylurea was obtained in 91% yield in the presence of 5.0 equivs. of KOH (Table 1, Run 8). It is noteworthy that carbonylation of nitrobenzene hardly proceeded in the absence of selenium (Table 1, Run 10).

The present DPU synthetic methodology was applied to substituted nitroarenes and symmetrical substituted 1,3-diarylureas were also obtained in good yields [Table 2 and Eq. (2)]. Both KOH and NaOAc could be used as the co-catalysts for the carbonylation of substituted nitroarenes, leading to varying conversions of the nitroarenes and yields of the 1,3-diarylurea products (Table 2). Complete conversion was achieved for 4-alkylbenzenes in the presence of KOH (Runs 1, 7 and 9), while only partial conversion of the substrates was observed under the same conditions when using NaOAc as the base (Table 2, Runs 2, 8 and 10). In several cases using KOH as the base complete conversions of the substrates were observed with low yields of symmetrical ureas (Table 2, Runs 1 and 9), while the same substrates afforded the urea products in high yields when using NaOAc (Table 2, Runs 2 and 10). It is unclear why no obvious reaction occurred with 2-methoxynitrobenzene under the same reaction conditions (Table 2, Run 13). Small amounts of substituted anilines could be detected in the resultant reaction mixtures, but the predominant by-products from the reactions were oligomers and/or polymers of anilines, and some unidentified colloidal compounds (Table 2, Runs 1 and 9).[13,14]



(2)

Conversions of the substrates and isolated yields of the products, i.e., symmetrically substituted 1,3-diarylureas varied depending on the substituent alkyls on the phenyl rings (Table 2, Runs 1–11). The electron-donating property of 4-positioned alkyl or alkoxy groups on the phenyl rings made the nitro group more reactive than those of the 3- and 2-substituted analogues, resulting in faster conversion of the substrates. The steric effects of 3- and 2-positioned alkyl or alkoxy groups on phenyl rings may be attributed to the lower conversions of nitroarenes under the same conditions. Up to 100% conversions for alkyl- and alkoxy-substituted nitroarenes and 94% isolated yields of symmetrical 1,3-diarylureas were achieved (Table 2, Runs 1–17). It is noteworthy that 2-methoxynitrobenzene hardly proceeded to form the desired symmetrical urea product (Table 2, Runs 14 and 15) and 2-methylnitrobenzene did not reach a decent conversion and yield of the product either (Table 2, Runs 5 and 6) due to steric hindrance. The presence of potassium hydroxide led to nuleophilic substitution reactiosn of the chloride on the phenyl ring by the $N(CH_3)_2$ moiety of DMF under the reaction conditions, resulting in N,N′-dimethyl-4-nitroaniline as the major product from the reaction of 4-chloronitrobenzene (Table 2, Run 18). Thus, NaOAc was used as the co-catalyst for the carbonylation of halo-substituted nitrobenzenes (Table 2, Runs 19–23). The electron-withdrawing property of the 4-Cl moiety on the substituted phenyl ring made the nitro group of the substrate less reactive so that no obvious reaction occurred for 4-chloronitrobenzene under the reaction conditions (Table 2, Run 19). However, 3-chloronitrobenzene, 4-methyl-3-chloronitrobenzene and 2-methyl-3-chloronitrobenzene as well as 3-bromonitrobenzene demonstrated fairly good reactivity to afford their corresponding symmetrical urea products in fair to good yields (60–89%) (Table 2, Runs 20–23). 3-Trifluoromethylnitrobenzene was transformed into its corresponding symmetrical urea in moderate yields (59–60%) (Table 2, Runs 24 and 25).

A reaction process involving a phase transfer catalysis phenomenon was presented during the above-discussed reactions.[11b, e] Prior to the introduction of CO into the reaction mixture, the catalytic system was heterogeneous and the catalyst selenium was observed as a powder. As the reaction proceeded the selenium was completely dissolved to a red species and the system became homogeneous. When the reaction was quenched by stopping the bubbling of CO and exposing the reaction mixture to air, the red selenium species was oxidized by air to

Table 2. Carbonylation of substituted nitroarenes to 1,3-diarylureas.

Run	R	Base	Time [h]	Conversion [%][a]	Yield [%][b]
1	4-Me	KOH	12	100	20
2	4-Me	NaOAc	13	90	81
3	3-Me	KOH	13	86	78
4	3-Me	NaOAc	13	88	82
5	2-Me	KOH	13	51	42
6	2-Me	NaOAc	13	38	21
7	4-Et	KOH	12	100	91
8	4-Et	NaOAc	13	85	79
9	4-*i*-Pr	KOH	12	100	79
10	4-*i*-Pr	NaOAc	13	97	94
11	3-*i*-Pr	NaOAc	13	70	63
12	4-OMe	KOH	13	77	69
13	4-OMe	NaOAc	13	45	31
14	2-OMe	KOH	10	<5	–
15	2-OMe	NaOAc	10	5	<5
16	4-OEt	KOH	10	95	91
17	4-OEt	NaOAc	12	98	87
18	4-Cl	KOH	13	48	44[c]
19	4-Cl	NaOAc	13	<5	–
20	3-Cl	NaOAc	9	100	84
21	3-Cl,4-Me	NaOAc	12	100	89
22	2-Me,3-Cl	NaOAc	12	71	60
23	3-Br	NaOAc	12	73	64
24	3-CF_3	KOH	13	70	60
25	3-CF_3	NaOAc	13	71	59

Reaction conditions: nitroaromatic, 15 mmol; bubbling CO, 20 mL/min; base, 5.0 mmol; H_2O, 0.5 mL (27.7 mmol); selenium, 0.030 g (0.38 mmol); DMF, 10 mL; 95 °C.

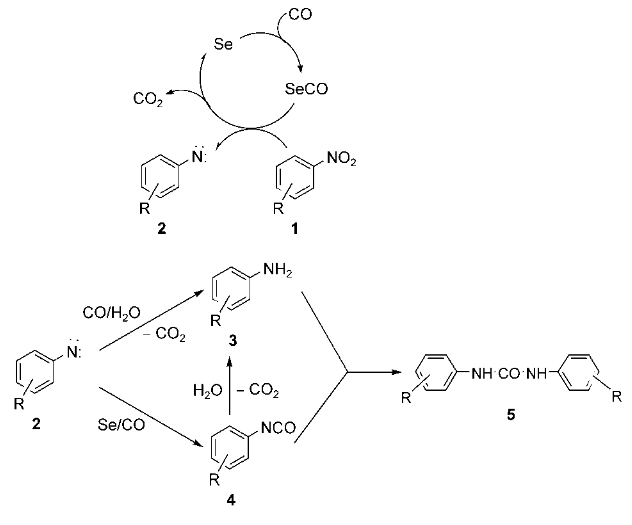
[a] Determined by HPLC and/or TLC.

[b] Yield of isolated product.

[c] The product is *N,N′*-dimethyl-4-nitroaniline.

form a grey selenium precipitate which can be easily recovered by filtration and reused to demonstrate a catalytic activity similar to that of fresh elemental selenium. These results suggest that the present catalytic system is bestowed with advantages of both homogeneous and heterogeneous catalysis. Although a detailed study of the reaction mechanism has not been undertaken, the present reactions can be mechanistically understood *via* the reaction pathway proposed in Scheme 1. *In situ* generated carbonyl selenide (SeCO)[15] from elemental selenium and CO is the catalytic species and deoxygenation of nitroaromatic **1** with SeCO results in the reactive intermediate nitrene **2** and carbon dioxide. Nitrene **2** reacts with H_2O in the presence of CO to form aniline **3**, with CO and/or SeCO to afford isocyanate **4**. Isocyanate **4** further reacts with aniline or nitrene **2** to give the symmetrical urea **5**.

In conclusion, we have developed a protocol for the production of symmetrical 1,3-diarylureas by a direct, non-metallic, selenium-catalyzed carbonylation of nitroarenes with CO under atmospheric pressure. The present one-pot synthesis of symmetrical ureas represents a new application of CO under selenium catalysis.



Scheme 1.

Experimental Section

General Procedure

A 50-mL three-necked flask was fitted with a condenser and charged with nitroarene (15 mmol), base (5.0 mmol), H_2O (0.5 mL), selenium (0.38 mmol), and DMF (10 mL), and was then placed in an oil bath preheated at 95 °C. Carbon monoxide (20 mL/min) was bubbled into the reaction mixture with vigorous stirring for the stated time. After cooling to ambient temperature, the resultant mixture was exposed to air and further stirred for about two hours. The mixture was filtered to recover selenium and water (50 mL) was then poured into the filtrate to precipitae the crude product. Purification by column chromatography on silica gel using Et_2O-AcOEt (20:1 to 10:1) as the eluent afforded the urea product. Products were identified by NMR and HPLC-MS measurements and/or comparison with authentic samples.

Acknowledgements

We are grateful for financial support from the Innovation Funding of the Chinese Academy of Sciences, P. R. China.

References and Notes

[1] T. P. Vishnyakova, I. A. Golubeva, E. V. Glebova, *Russ. Chem. Rev. (Engl. Edn.)* **1985**, *54*, 249.

[2] M. B. Smith, J. March, *March's Advanced Organic Chemistry*, 5th edn., Wiley, New York, **2001**, p. 1191; H. J. Knölker, T. Braxmeier, G. Schlechtingen, *Angew. Chem. Int. Ed.* **1995**, *34*, 2497.

[3] P. Majer, R. S. Randad, *J. Org. Chem.* **1994**, *59*, 1937.

[4] T. M. Flyes, T. D. James, A. Pryhitka, M. Zojsji, *J. Org. Chem.* **1993**, *58*, 7456; M. Lamothe, M. Perez, V. Colovray-Gotteland, S. Halazy, *Synlett* **1996**, 507.

[5] L. E. Overman, G. F. Taylor, C. B. Petty, P. J. Jessup, *J. Org. Chem.* **1978**, *43*, 2164.

[6] For a recent review on synthesis of ureas, see: F. Bigi, R. Maggi, G. Startori, *Green Chem.* **2000**, *2*, 140.

[7] For selected recent papers describing carbonylation of nitroarenes, see: a) S. M. Islam, D. Mal, B. K. Palit, C. R. Saha, *J. Mol. Catal. A: Chem.* **1999**, *142*, 169; b) P. Wehman, L. Borst, P. C. J. Kamer, P. W. N. M. van Leeuwen, *J. Mol. Catal. A*: *Chem.* **1996**, *112*, 23; c) B. Ridone, A. Bassoli, S. Cenini, *J. Mol. Catal.* **1991**, *66*, 163; d) A. M. Tafesh, J. Weiguny, *Chem. Rev.* **1996**, *96*, 2035.

[8] For selected recent papers regarding synthesis of ureas by oxidative carbonylation, see: a) B. Gabriele, R. Mancuso, G. Salerno, M. Costa, *Chem. Commun.* **2003**, 486; b) S. A. R. Mulla, C. V. Rode, A. A. Kelkar, S. P. Gupte, *J. Mol. Catal. A*: *Chem.* **1997**, *122*, 103; c) F. Qian, J. E. McCusker, Y. Zhang, A. D. Main, M. Chlebowski, M. Kokka, L. McElwee-White, *J. Org. Chem.* **2002**, *67*, 4086; d) T. Kihlberg, F. Karimi, B. Langström, *J. Org. Chem.* **2002**, *67*, 3687; e) F. Shi, Y. Deng, T. SiMa, H. Yang, *Tetrahedron Lett.* **2001**, *42*, 2161.

[9] X. Z. Liu , S. W. Lu, *Chem. Lett.* **2003**, *32*, 1142.

[10] T. Miyata, K. Kondo, S. Murai, N. Sonoda, *Angew. Chem. Int. Ed.* **1980**, *19*, 1008.

[11] a) Y. Yang, S. W. Lu, *Tetrahedron Lett.* **1999**, *40*, 4845; b) J. T. Mei, Y. Yang. Y. Xue, S. W. Lu, *J. Mol.* Catal. *A*: *Chem.* **2003**, *191*, 135; c) G. Ling, J. Z. Chen, S. W. Lu, *J. Mol.* Catal. *A*: *Chem.* **2003**, *202*, 23; d) J. Z. Chen, G. Ling, S. W. Lu, *Tetrahedron* **2003**, *59*, 8251; e) J. Z. Chen, G. Ling, S. W. Lu, *Eur. J. Org. Chem.* **2003**, *17*, 3446.

[12] For selected papers on Se-catalyzed reactions, see: a) N. Sonoda, T. Yasuhara, K. Kondo, T. Ikeda, S. Tsutsumi, *J. Am. Chem. Soc.* **1971**, *93*, 6344; b) N. Sonoda, *Pure Appl. Chem.* **1993**, *65*, 699; c) H. S. Kim, Y. J. Kim, H. J. Lee, M. J. Chung, S. D. Lee, *U. S. Patent* 6,127,575, **1999**; d) H. S. Kim, Y. J. Kim, H. Lee, S. D. Lee, C. S. Chin, *J. Catal.* **1999**, *184*, 526.

[13] T. Alam, H. Tarannum, M. N. V. Ravi Kumar, Kamaluddin, *Talanta* **2000**, *51*, 1097.

[14] G. B. Hix, V. C. Maddocks, K. D. M. Harris, *Polyhedron* **2000**, *19*, 765.

[15] a) K. Kondo, S. Yokoyama, N. Miyoshi, S. Murai, N. Sonoda, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 691; b) K. Kondo, S. Yokoyama, N. Miyoshi, S. Murai, N. Sonoda, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 692.