

Synthesis of Indoles: Selenium-Catalyzed Reductive *N*-Heterocyclization of 2-Nitrostyrenes with Carbon Monoxide

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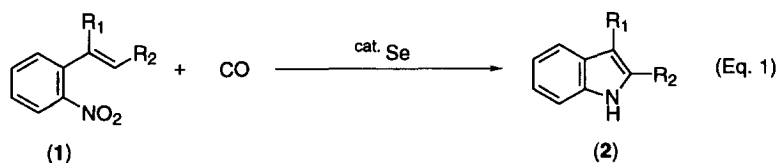
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Abstract: Reductive *N*-heterocyclization of 2-nitrostyrenes with carbon monoxide in the presence of a catalytic amount of selenium proceeded efficiently to afford the corresponding indoles in moderate to good yields. © 1999 Elsevier Science Ltd. All rights reserved.

In view of the industrial and agricultural applications and biological and analytical importance of indoles,¹⁾ the synthesis of these compounds has been the subject of research for over one hundred years. Until recently, indole syntheses relied primarily on well-established methods such as the Fischer indole synthesis, the Madelung cyclization of *N*-acyl-*o*-toluidines, the reductive cyclization of *o*-nitrobenzyl ketones, the Leimgruber-Batcho synthesis from *o*-nitrotoluenes and dimethylformamide acetal and the Gassman synthesis from *N*-halo anilines.²⁾

Carbon monoxide is widely accepted as a useful reducing agent as well as an extremely important agent for introducing carbonyl function into organic molecules.³⁾ As one application of carbon monoxide in organic synthesis, the transition metal-catalyzed reductive carbonylation of organic nitro compounds with carbon monoxide has been developed.⁴⁾ In view of the proposed reaction pathway of transition metal-catalyzed reductive carbonylation of nitro compounds with carbon monoxide, the construction of the indole skeleton *via* reductive deoxygenation of 2-nitro substituted arenes with carbon monoxide as a reducing agent has emerged as a versatile method for the synthesis of indoles. In fact, various approaches have been reported for this transformation using transition metal compounds containing palladium,⁵⁾ iron,⁶⁾ ruthenium⁶⁾ or rhodium⁶⁾ as the catalyst.

We have disclosed that elemental selenium is an efficient catalyst for the carbonylation and the reduction of various organic compounds with carbon monoxide in the presence of a tertiary amine.⁷⁾ In connection with ongoing investigations into the selenium-catalyzed transformation of various organic compounds with carbon monoxide, it has been found that selenium catalyzed the reductive *N*-heterocyclization of 2-nitrostyrenes with carbon monoxide, giving the corresponding indoles in moderate to good yields (Eq. 1).⁸⁾




The reaction conditions for the conversion of 2-nitrostilbene (**1a**) into 2-phenylindole (**2a**) were examined in detail and some of the results are shown in Table 1. When **1a** was treated with carbon monoxide (30 atm) in the presence of a catalytic amount of selenium (0.2 equiv.) and excess amounts of triethylamine (10 equiv.) in benzene solution at 140 °C for 24 h, reductive *N*-heterocyclization of **1a** occurred efficiently to give **2a** in 73 % yield (entry 1). A wide variety of solvents such as benzene, THF, acetonitrile, 1,4-dioxane, *n*-hexane and DMF are available for the transformation of **1a** into **2a** (entries 1-6). It is interesting to note that, when DMF was used as a solvent, the reaction of **1a** proceeded smoothly under mild conditions (CO (5 atm) at 100 °C for 5 h) to afford **2a** in 76 % yield (entry 7).⁹ The yields of **2a** were also dramatically affected by the amine used (entries 8 and 10-12). The use of *N*-methylpyrrolidine, DBN or DBU instead of triethylamine caused a distinct decrease in the yield of **2a** owing to the reduction of the nitro group to an amino group (entries 10-12). In this reaction, a smaller amount of selenium (5 mol%) was also effective with prolonged reaction time (15 h) to give **2a** in 85 % yield (entry 9).

In order to know the scope and limitation of the selenium-catalyzed reductive *N*-heterocyclization of 2-nitrostyrenes with carbon monoxide, a variety of 2-nitrostyrenes were allowed to react with carbon monoxide using triethylamine as the amine in the presence of a catalytic amount of selenium in DMF solvent and the results are shown in Table 2. The reductive *N*-heterocyclization of 2-nitro-4'-methyl-, 2-nitro-4'-methoxy- and 2-nitro-4'-trifluoromethylstilbene also occurred efficiently to produce the corresponding indoles in 65, 72 and 78 % yields, respectively (entries 1-3). However, the reaction of 2-nitrostyrene was not completed under the same reaction conditions as that of **1a** to provide the indole in only 30 % yield along with the recovered starting material (62%). The yield of indole was improved by the reaction under higher pressure of CO (30 atm) at 140 °C for 24 h (entry 4). On the other hand, 2-(1-Propenyl)- and 2-(1-methyl-1-ethenyl)nitrobenzene were smoothly converted under CO (5 atm) at 100 °C for 24 h into the 2-methyl- and 3-methylindoles in 70 and 69 % yields, respectively (entries 5 and 6).

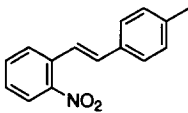
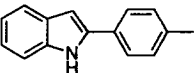
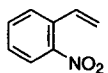

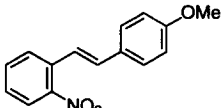
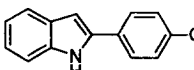
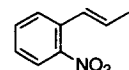
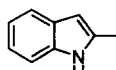
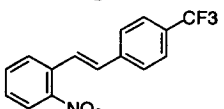
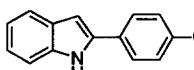
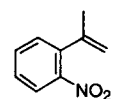
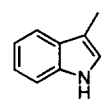
We previously have found a convenient preparation method of carbonyl selenide (SeCO), which involved acid-catalyzed decomposition of ammonium salts of selenocarbamates generated by the reaction of elemental selenium with carbon monoxide and secondary amine.¹⁰ We proposed, therefore, that the reaction starts with the deoxygenation of 2-nitrostyrenes with SeCO prepared from elemental selenium and carbon monoxide to generate the corresponding short-lived nitrene or nitrenoid species.¹¹ In this reaction, intramolecular insertion

Table 1. Selenium-Catalyzed Reductive *N*-Heterocyclization of 2-Nitrostilbene (**1a**) to 2-Phenylindole (**2a**) with Carbon Monoxide under Various Reaction Conditions^{a)}

Entry	Amine	Solvent	Yield / % ^{b)}
1	Et ₃ N	Benzene	73
2	Et ₃ N	THF	71
3	Et ₃ N	CH ₃ CN	70
4	Et ₃ N	1,4-Dioxane	60
5	Et ₃ N	<i>n</i> -C ₆ H ₁₄	46
6	Et ₃ N	DMF	72
7 ^{c)}	Et ₃ N	DMF	76
8 ^{d)}	Et ₃ N	DMF	80
9 ^{e)}	Et ₃ N	DMF	85
10	 N-Me	DMF	53
11 ^{c)}	DBN	DMF	13
12 ^{c)}	DBU	DMF	12

a) Reaction conditions : 2-Nitrostilbene (0.5 mmol), Se (0.1 mmol), solvent (5 ml), amine (5 mmol) and CO (30 atm) at 140 °C for 24h b) GC yield c) CO (5 atm) at 100 °C for 5 h d) CO (5 atm) at 140 °C for 5 h e) Se (0.025 mmol) at 100 °C for 15 h.

Table 2. Synthesis of Various Indoles^{a)}

Entry	Substrate	Product	Yield / % ^{b)}	Entry	Substrate	Product	Yield / % ^{b)}
1			65	4 ^{c)}			55
2			72	5 ^{d)}			70
3			78	6 ^{d)}			69

a) Reaction conditions : Substrate (0.5 mmol), Se (0.1 mmol), Et₃N (5 mmol), DMF (5 ml) and CO (5 atm) at 100 °C for 5 h.
 b) GC yield. c) CO (30 atm) at 140 °C for 24 h. d) At 100 °C for 24 h.

of nitrene or nitrenoid species, which was generated *in situ* by deoxygenation of the nitro group with SeCO, into the vinylic C-H bond at the *o*-position of the nitro group proceeded efficiently to produce indoles.^{13,14)}

In summary, we have succeeded in the synthesis of indoles *via* the reductive *N*-heterocyclization of 2-nitrostyrenes with carbon monoxide using selenium as a catalyst. Further studies on the synthetic application and the mechanism of these reactions are in progress.

Acknowledgement

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- 8) A typical procedure is as follows: in a 50 mL stainless steel autoclave were placed 2-nitrostilbene (113 mg, 0.5 mmol), selenium (8 mg, 0.1 mmol), triethylamine (555 mg, 5 mmol) and DMF (5 mL) and a magnetic stirring bar. The apparatus was flushed several times with carbon monoxide and charged at 5 atm. The mixture was heated at 100 °C with magnetic stirring for 5 h. After the reaction, carbon monoxide was purged in a well-ventilated hood, and the resulting mixture was extracted with diisopropyl ether (25 mL x 3). The organic layer was dried over MgSO₄ and evaporation of the solvent gave a yellow residue, which was chromatographed on silica gel to give 2-phenylindole in 76 % yield.
- 9) In the case of sulfur, the reaction of **1a** was not completed under the same reaction conditions as that of selenium to afford **2a** in only 19 % yield. On the other hand, tellurium showed no catalytic activity in this reaction at all.
- 10) K. Kondo, S. Yokoyama, N. Miyoshi, S. Murai, N. Sonoda, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 691.
- 11) It is generally considered that the the transition metal-catalyzed reductive carbonylation of nitro compounds with carbon monoxide involves the generation of a nitrene species, either free or coordinated to the metal, as a key intermediate.^{4d,4e,12)}
- 12) S. Cenini, C. Crotti, In *Metal Promoted Selectivity in Organic Synthesis*; Kluwer Academic Publishers: Netherlands, **1991** and references therein.
- 13) The generation of carbon dioxide was ascertained by the bubbling of the resulting gas into the aq. Ba(OH)₂.
- 14) The insertion of nitrene to the vinylic C-H bonds is well known and various synthetic applications have been developed.¹⁵⁾
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