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LETTERS

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

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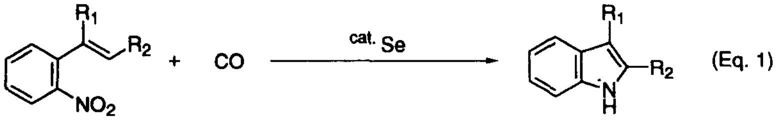
Abstract: Reductive *N*-heterocyclization of 2-nitrostyrenes with carbon monoxide in the presence of a catalytic amount of selenium proceeded efficiently to afford the corresponding indoles in moderate to good yields. © 1999 Elsevier Science Ltd. All rights reserved.

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)



(1) **(2)**

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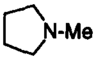
The reaction conditions for the conversion of 2-nitrostilbene (**1a**) into 2-phenylindole (**2a**) were examined in detail and some of the results are shown in Table 1. When **1a** was treated with carbon monoxide (30 atm) in the presence of a catalytic amount of selenium (0.2 equiv.) and excess amounts 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).

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

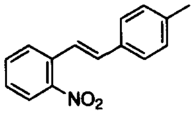
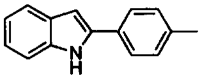
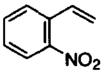
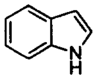
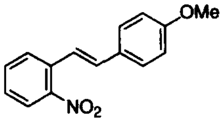
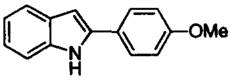
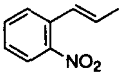
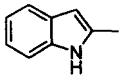
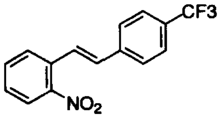
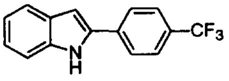
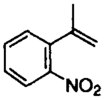
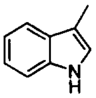
Entry	Amine	Solvent	Yield / %[b]
1	Et_3N	Benzene	73
2	Et_3N	THF	71
3	Et_3N	CH_3CN	70
4	Et_3N	1,4-Dioxane	60
5	Et_3N	n-C_6H_{14}	46
6	Et_3N	DMF	72
7[c]	Et_3N	DMF	76
8[d]	Et_3N	DMF	80
9[e]	Et_3N	DMF	85
10	 N-Me	DMF	53
11[c]	DBN	DMF	13
12[c]	DBU	DMF	12

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.

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 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), Et_3N (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.

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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 $MgSO_4$ 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)

15) In *Nitrenes*; W. Lwowski, John Wiley & Sons: New York, **1970** and references therein.