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Novel Synthesis of Indoles via Palladium-Catalyzed Reductive N-Heterocyclization of *o*-Nitrostyrene Derivatives

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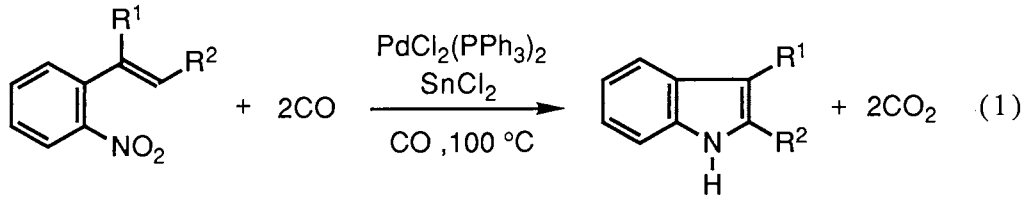
Indole derivatives were readily prepared from the reductive N-heterocyclization of *o*-nitrostyrene derivatives in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$ - $SnCl_2$ under carbon monoxide pressure (20 kg/cm^2) at 100 °C for 16 h. With *o*-nitrostilbene, 2-phenylindole was obtained in 75% yield.

The Fischer indole synthesis is most widely used to construct an indole skeleton and has been extensively reviewed.[1] Recently, numerous synthetic approaches to construction of indole skeleton using transition-metal catalysts, particularly palladium ones.[2,3]

Among the various possible methods, we are interested in transition-metal complex-catalyzed reductive N-heterocyclization of nitro compounds.[3,4] Herein, we report a novel and facile synthesis of indoles via palladuim-catalyzed reductive N-heterocyclization of *o*-nitrostyrene derivatives under relatively mild reaction conditions (Eq. 1).



(1)

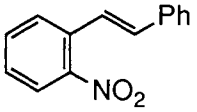
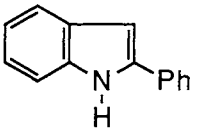
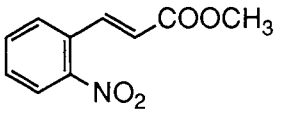
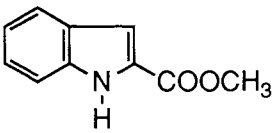
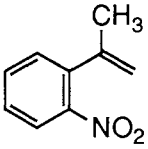
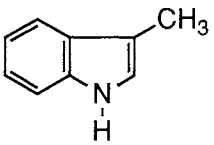
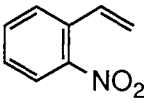
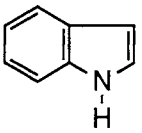
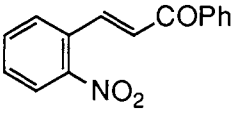
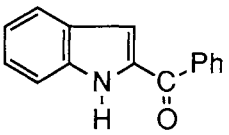
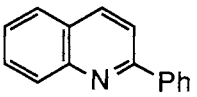
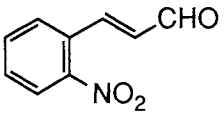
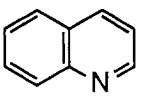
In a typical experiment, a mixture of *o*-nitrostyrene derivative (2.0 mmol), $PdCl_2(PPh_3)_2$ (0.10 mmol), and $SnCl_2$ (1.0 mmol) in 1,4-dioxane (10 ml) was stirred at 100 °C for 16 h under carbon monoxide pressure (20 kg/cm^2). All products were isolated by Kugelrohr distillation, and satisfactory spectroscopic and analytical data of them were obtained.

A wide variety of *o*-nitrostyrene derivatives bearing alkyl, aryl, and alkoxycarbonyl group on olefinic carbons were smoothly transformed into the corresponding indoles in 50 - 75% yields (runs 1-4 in Table 1). On the other hand, in the case of *o*-nitrochalcone which has an acyl group on the olefinic carbon, 2-benzoylindole was obtained in 52% yield, together with 2-phenylquinoline in 34%

yield (run 5). In the reaction of *o*-nitrocinnamaldehyde, only quinoline was isolated in 23% yield and the corresponding indole derivative was not obtained at all (run 6) (*vide infra*).

Furthermore, *o*-nitrobiphenyl did not convert into carbazole under the present reaction conditions, and even at 150 °C.

Table 1. Reductive N-Heterocyclization of *o*-Nitrostyrene Derivatives

Run	Substrate	Product	Yield/%[a)]
1			75 (74)
2			62 (60)
3			57 (41)
4			50
5			52
			34
6			(23)

a) GLC yields (figures in parentheses were isolated yields).

Catalytic activity of several transition-metal complexes was examined with methyl *o*-nitrocinnamate as a substrate, and the results are summarized in Table 2.

In the present reaction, the combination of $PdCl_2(PPh_3)_2$ with $SnCl_2$ was essential for the catalytic activity (runs 2, 7, and 8). Other additives such as $SnCl_4$, $CuCl_2$, $FeCl_3$, $ZnCl_2$, and $BF_3 \cdot Et_2O$ were ineffective. Phosphorus ligands such as triphenylphosphine and tributylphosphine were also indispensable for high catalytic

activity (runs 11-14). The catalytic activity of other group VIII metal complexes was relatively low (runs 16-19).

Table 2. Catalytic Activity of Several Transition Metal Complexes[a)]

Run	Catalyst	Additive	Conv./%	Yield/%
2	$PdCl_2(PPh_3)_2$	$SnCl_2$	100	62
7	$PdCl_2(PPh_3)_2$	-	4	3
8	-	$SnCl_2$	31	7
9	$Pd(PPh_3)_4$	-	52	39
10	$Pd(PPh_3)_4$	$SnCl_4$	24	8
11	$PdCl_2(PBu_3)_2$	$SnCl_2$	81	61
12	$PdCl_2$(bipy)	$SnCl_2$	16	8
13	$PdCl_2(PhCN)_2$	$SnCl_2$	14	10
14[b)]	$PdCl_2(PhCN)_2$ +PPh_3	$SnCl_2$	96	52
15[b)]	PPh_3	$SnCl_2$	30	10
16	$PtCl_2(PPh_3)_2$	$SnCl_2$	44	32
17	$NiCl_2(PPh_3)_2$	$SnCl_2$	31	8
18	$RuCl_2(PPh_3)_3$	$SnCl_2$	25	16
19	$RhCl(PPh_3)_3$	$SnCl_2$	24	15

a) Methyl *o*-nitrocinnamate (2.0 mmol), catalyst (0.10 mmol), additive (1.0 mmol), 1,4-dioxane (10 ml), CO 20 kg/cm^2, 100 °C, 16 h. b) Triphenylphosphine (0.20 mmol) was added.

The present reaction may be rationalized by assuming a nitrene intermediate.[5)] Firstly, deoxygenation of the nitro group in *o*-nitrostyrene derivative by carbon monoxide would occur to give the corresponding nitrene intermediate. This electrophilic nitrene could attack the olefinic carbon, followed by a subsequent hydrogen transfer reaction to give the corresponding indole. In the case of *o*-nitrochalcone, reductive coupling of the nitro group with the carbonyl group competed with the formation of indoles, and in the case of *o*-nitrocinnamaldehyde, only reductive coupling of the nitro group with the carbonyl group predominantly occurred.[6)]

Indeed, after the reductive N-heterocyclization reaction of methyl *o*-nitrocinnamate (run 2), CO_2 evolved into a gas phase was detected in 141% yield based on the amount of methyl *o*-nitrocinnnamate. This result suggests that carbon monoxide actually operated as an efficient reducing agent of the nitro group.[7)]

Further studies on the mechanism and attempts to apply the present reaction to organic synthesis are in progress.

References

1) B. Robinson, *Chem. Rev.*, **63**, 373 (1963); **69**, 227 (1969).

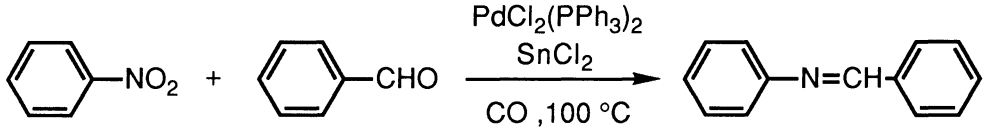
2) L. S. Hegedus, *Angew. Chem., Int. Ed. Engl.*, **27**, 1113 (1988) and references cited therein; R. C. Larock and E. K. Yum, *J. Am. Chem. Soc.*, **113**, 6689 (1991).

3) Cenini et al. have already reported transition-metal carbonyls catalyzed synthesis of indoles via deoxygenation of *o*-nitrostyrene derivatives, but the reaction conditions were extremely severe and a considerable amount of *o*-aminostyrene derivatives was obtained as a by-product. See; C. Crotti, S. Cenini, B. Rindone, S. Tollari, and F. Demartin, *J. Chem. Soc., Chem. Comm.*, **1986**, 784; C. Crotti, S. Cenini, R. Todeschini, S. Tollari, *J. Chem. Soc., Faraday Trans.*, **87**, 2811 (1991).

4) We have also reported transition-metal complex-catalyzed synthesis of several N-heterocyclic compounds via reductive N-heterocyclization reaction. For examples; M. Akazome, T. Kondo, and Y. Watanabe, *J. Chem. Soc., Chem. Comm.*, **1991**, 1466; Y. Watanabe, N. Suzuki, Y. Tsuji, S. C. Shim, and T. Mitsudo, *Bull. Chem. Soc. Jpn.*, **55**, 1116 (1982); Y. Watanabe, N. Suzuki, and Y. Tsuji, *ibid.*, **55**, 2445 (1982).

5) S. Bhaduri, H. Khwaja, N. Sapre, K. Sharma, A. Basu, P. G. Jones, and G. Carpenter, *J. Chem. Soc., Dalton Trans.*, **1990**, 1313; S. Cenini, C. Crotti. M. Pizzotti, and F. Porta, *J. Org. Chem.*, **53**, 1243 (1988); E. Alessio and G. Mestroni, *J. Organomet. Chem.*, **291**, 117 (1985); Y. Watanabe, Y. Tsuji, R. Takeuchi, and N. Suzuki, *Bull. Chem. Soc. Jpn.*, **56**, 3343 (1983); F. J. Weigert, *J. Org. Chem.*, **38**, 1316 (1973); J. E. Kmiecik, *ibid.*, **30**, 2014 (1965); R. J. Sundberg, L-S. Lin, and D. E. Blackburn, *J. Heterocycl. Chem.*, **6**, 441 (1969); P. J. Bunyan and J. I. G. Cadogan, *J. Chem. Soc.*, **1963**, 42; R. A. Abramovitch and B. A. Davis, *Chem. Rev.*, **64**, 149 (1964).

6) The present system ($PdCl_2(PPh_3)_2$ - $SnCl_2$) also catalyzed the reductive coupling reaction of nitrobenzene with benzaldehyde to give N-benzylideneaniline in 71% GLC yield (Eq. 2). This result suggests that the quinoline derivatives would be obtained by *intramolecular* reductive coupling reaction of nitro groups with carbonyl groups, after *trans-cis* isomerization of olefinic carbon-carbon double bond.



(2)

(2.1 mmol) (2.5 mmol) 71% yield

7) Under hydrogen pressure(20 kg/cm^2), the present reductive N-heterocyclization reaction did not proceed at all.

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