Communications

Ruthenium Complex-Catalyzed Reductive *N*-Heterocyclization: Novel Synthesis of 1-Pyrroline Derivatives from γ-Nitrocarbonyl Compounds

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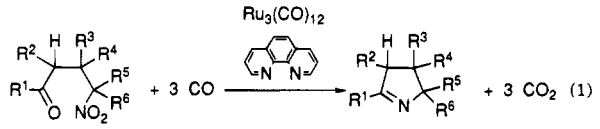
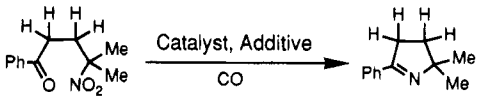
The transition metal complex-catalyzed synthesis of *N*-heterocyclic compounds has been the subject of much investigation and development in recent years[1] because of the biological activity associated with many fundamental heterocyclic skeletons. In the context of our studies of *N*-heterocyclization reactions,[2] our attention has recently been focused on the deoxygenating capability of carbon monoxide. Palladium and ruthenium complex-catalyzed reductive *N*-heterocyclizations of nitroarenes have been developed[3] which have been assumed to proceed *via* active transition metal nitrene intermediates. These would be generated by selective deoxygenation of the nitro group by carbon monoxide. In these reactions, however, only nitroarenes have been tested as starting materials. Here, we report a novel synthesis of 1-pyrroline derivatives by the transition metal complex-catalyzed reductive *N*-heterocyclization of aliphatic γ-nitrocarbonyl compounds (eq 1).



1a:R^1=Ph;R^2,R^3,R^4=H;R^5,R^6=Me **2a**
1b:R^1=Ph;R^2,R^3,R^4=H;R^5,R^6=Et **2b**
1c:R^1,R^5,R^6=Me;R^2,R^3=H;R^4=Ph **2c**
1d:R^1,R^5=Me;R^2,R^3,R^4=H;R^6=Ph **2d**

The catalytic activities of several transition metal complexes were examined in the reaction of 4-methyl-4-nitro-1-phenyl-1-pentanone (**1a**) (Table 1). Under 20 kg cm^{-2} of initial CO pressure at 120 °C, a $Ru_3(CO)_{12}$/1,10-phenanthroline system showed considerable catalytic activity, and 5,5-dimethyl-2-phenyl-1-pyrroline (**2a**) was obtained in 50% yield (entry 1). When only $Ru_3(CO)_{12}$ was employed without 1,10-phenanthroline at 120 °C, no product was obtained (entry 2). In addition, a $PtCl_2(PPh_3)_2$–$SnCl_2$ system showed only moderate catalytic activity (entry 5). The $PdCl_2(PPh_3)_2$–$MoCl_5$ or $SnCl_2$ systems (entries 3 and 4), which effectively catalyzed the synthesis of 2*H*-indazole,[3a,c] indole,[3b,c] and quinazoline[3e] derivatives *via* the reductive *N*-heterocyclization of nitroarenes, showed only low activity.

Table 1. Catalytic Activities of Several Transition-Metal Complexes for Reductive *N*-Heterocyclization of 4-Methyl-4-nitro-1-phenyl-1-pentanone[a]



entry	catalyst	additive	convn[b]/%	yield[b]/%
1	$Ru_3(CO)_{12}$	1,10-phenanthroline	100	50
2	$Ru_3(CO)_{12}$		21	0
3	$PdCl_2(PPh_3)_2$	$MoCl_5$	100	23
4	$PdCl_2(PPh_3)_2$	$SnCl_2$	80	20
5	$PtCl_2(PPh_3)_2$	$SnCl_2$	100	46

[a] 4-Methyl-4-nitro-1-phenyl-1-pentanone (2.0 mmol), catalyst (0.10 mmol), additive (1.0 mmol), 1,4-dioxane (10 mL), under CO (20 kg cm^{-2}) at 120 °C for 16 h. [b] Determined by GLC.

In the $Ru_3(CO)_{12}$-catalyzed reactions, the effects of ligands were examined (Table 2). Under 40 kg cm^{-2} of initial CO pressure at 140 °C, the combination of $Ru_3(CO)_{12}$ and 1,10-phenanthroline proved effective for the reductive *N*-heterocyclization of γ-nitrocarbonyl compounds and showed the best catalytic activity (entry 6). When 2,9-disubstituted 1,10-phenanthrolines were employed, the yield of product decreased (entries 9 and 10). 2,2′-Bipyridine was moderately effective (entry 11). Other monodentate, aliphatic, or phosphorus ligands performed poorly in this reductive *N*-heterocyclization (entries 12–17).

Representative results of the syntheses of 1-pyrroline derivatives are summarized in Table 3. γ-Nitrocarbonyl compounds were smoothly transformed into the corresponding 1-pyrroline derivatives in 78–91% yield (entries 6 and 18–20).[4] To our knowledge, the present reaction is the first example of the catalytic synthesis of 1-pyrroline derivatives.

Several reducing agents were examined in this reductive *N*-heterocyclization of γ-nitrocarbonyl compounds.

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(2) For example, see: (a) Watanabe, Y.; Suzuki, N.; Tsuji, Y.; Shim, S. C.; Mitsudo, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1116 and references cited therein. (b) Watanabe, Y.; Suzuki, N.; Tsuji, Y. *Ibid.* **1982**, *55*, 2445. (c) Tsuji, Y.; Huh, K.-T.; Watanabe, Y. *J. Org. Chem.* **1987**, *52*, 1673. (d) Tsuji, Y.; Kotachi, S.; Huh, K.-T.; Watanabe, Y. *J. Org. Chem.* **1990**, *55*, 580 and references cited therein. (e) Kondo, T.; Yang, S.; Huh, K.-T.; Kobayashi, M.; Kotachi, S.; Watanabe, Y. *Chem. Lett.* **1991**, 1275.

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(4) **General Procedure.** A mixture of γ-nitrocarbonyl compound (2.0 mmol), $Ru_3(CO)_{12}$ (0.10 mmol), 1,10-phenanthroline (1.0 mmol), and dry 1,4-dioxane (10 mL) was placed in a 50 mL stainless steel autoclave (Yuasa Giken SUS 316) equipped with a glass liner and a magnetic stirring bar. The autoclave was sealed, and then the air was purged three times with 20 kg cm^{-2} pressurization–depressurization cycles of carbon monoxide. The reactor was then pressured to 40 kg cm^{-2} with carbon monoxide at room temperature and heated to 140 °C over 20 min with stirring, and the temperature was held for 16 h. The reaction was terminated by rapid cooling, and gaseous products were discharged. The resulting solution was analyzed by GLC and FT-IR. Conversions of the substrates and yields of the products were determined by GLC by means of internal standard method. The products were isolated by Kugelrohr distillation and/or preparative TLC (absorbent, silica gel; eluent, chloroform). The identification of the products were performed by ^{1}H- and ^{13}C-NMR, IR, GC–MS, and elemental analyses.

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Table 2. Effects of Ligands[a]

entry	catalyst	ligand	convn[b]/%	yield[b]/%
6	$Ru_3(CO)_{12}$	1,10-phenanthroline	100	91
7	$Ru_3(CO)_{12}$		100	2
8		1,10-phenanthroline	8	0
9	$Ru_3(CO)_{12}$	2,9-dimethyl-1,10-phenanthroline	100	54
10	$Ru_3(CO)_{12}$	2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline	100	21
11	$Ru_3(CO)_{12}$	2,2′-bipyridine	100	62
12	$Ru_3(CO)_{12}$	pyridine[c]	55	9
13	$Ru_3(CO)_{12}$	*N,N,N′,N′*-tetramethylethylenediamine	67	17
14	$Ru_3(CO)_{12}$	*N,N,N′,N′*-tetramethyl-1,3-propanediamine	58	7
15	$Ru_3(CO)_{12}$	triethylamine[c]	28	4
16	$Ru_3(CO)_{12}$	1,2-bis(dimethylphosphino)ethane	100	10
17	$Ru_3(CO)_{12}$	triphenylphosphine[c]	77	0

[a] 4-Methyl-4-nitro-1-phenyl-1-pentanone (2.0 mmol), $Ru_3(CO)_{12}$ (0.10 mmol), ligand (1.0 mmol), 1,4-dioxane (10 mL), under CO (40 kg cm^{-2}) at 140 °C for 16 h. [b] Determined by GLC. [c] 2.0 mmol.

Table 3. Synthesis of 1-Pyrroline Derivatives[a]

entry	substrate	product	yield[b]/%
6	**1a**	**2a**	91
18	**1b**	**2b**	81
19	**1c**	**2c**	86
20	**1d**	**2d**	78

[a] Substrate (2.0 mmol), $Ru_3(CO)_{12}$ (0.10 mmol), 1,10-phenanthroline (1.0 mmol), 1,4-dioxane (10 mL), under CO (40 kg cm^{-2}) at 140 °C for 16 h. [b] Determined by GLC.

After conduct of the reaction under 40 kg cm^{-2} of initial CO pressure, carbon dioxide was formed in the gas phase to the extent of 262%, based on the amount of γ-nitrocarbonyl compound (entry 6). This result is rationalized in terms of the generation of a ruthenium nitrene intermediate.[5] Whether under the water gas shift reaction conditions (CO: 40 kg cm^{-2} and water: 10 mmol), under hydrogen pressure (40 kg cm^{-2}), or under synthesis gas conditions (CO: 40 kg cm^{-2} and H_2: 40 kg cm^{-2}), the yield of **2a** was 3–4%. Consequently, carbon monoxide is the best reducing agent for the present reductive *N*-heterocyclization.

On the basis of the results mentioned above, the most plausible mechanism is as follows.[6] First, a zero-valent ruthenium–1,10-phenanthroline complex is formed.[7] Then, selective deoxgenation of the nitro group occurs to produce a ruthenium nitrene intermediate.[8] Subsequently, this active nitrene intermediate reacts with a carbonyl group in an intramolecular metathesis mode to give the corresponding 1-pyrroline derivatives and a ruthenium–oxo complex. The ruthenium–oxo complex is reduced to a zero-valent species by carbon monoxide,[9] completing the catalytic cycle. It is well-known that a nucleophilic nitrene complex reacts with the carbonyl group of aldehydes and ketones to yield the corresponding imines.[10] For example, McElwee-White et al. have reported that $(CO)_5W{=}NPh$ undergoes metathesis with aldehydes, ketones, and thioketones to give *N*-phenylimines, with the generation of carbon dioxide.[10c]

In conclusion, the transition metal complex-catalyzed reductive *N*-heterocyclization of nitroarenes by carbon monoxide[3] is adaptable to aliphatic nitro compounds by using a $Ru_3(CO)_{12}$/1,10-phenanthroline system, and this reaction provides a useful method for the synthesis of 1-pyrroline derivatives from γ-nitrocarbonyl compounds. Further studies on the mechanism and the application of this reductive *N*-heterocyclization to the synthesis of other *N*-heterocyclic compounds are in progress.

Supporting Information Available: Experimental procedures and compound characterization data (2 pages).

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(5) A similar reaction pathway was proposed in a previously reported reductive coupling and reductive carbonylation of aromatic nitro compounds catalyzed by transition-metal complexes. For example, see: (a) Kmiecik, J. E. *J. Org. Chem.* **1965**, *30*, 2014. (b) Iqbal, A. F. M. *Chemtech* **1974**, 566. (c) Alessio, E.; Mestroni, G. *J. Organomet. Chem.* **1985**, *291*, 117. (d) Cenini, S.; Crotti, C.; Pizzotti, M.; Porta, F. *J. Org. Chem.* **1988**, *53*, 1243. (e) Bassoli, A.; Cenini, S.; Farina, F.; Orlandi, M.; Rindone, B. *J. Mol. Catal.* **1994**, *89*, 121.

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(8) μ_3-Nitrene–ruthenium complexes were isolated in the reaction of $Ru_3(CO)_{12}$ with aromatic nitro compounds. (a) Sappa, E.; Milone, L. *J. Organomet. Chem.* **1973**, *61*, 383. (b) Bhaduri, S.; Gopalkrishman, K. S.; Sheldrick, G. M.; Clegg, W.; Stalke, D. *J. Chem. Soc., Dalton Trans.* **1983**, 2339. (c) Crotti, C.; Cenini, S.; Bassoli, A.; Rindone, B.; Demartin, F. *J. Mol. Catal.* **1991**, *70*, 175.

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