Transition-Metal Complex-Catalyzed Reductive N-Heterocyclization: Synthesis of 4(3*H*)-Quinazolinone Derivatives from *N*-(2-Nitrobenzoyl)amides

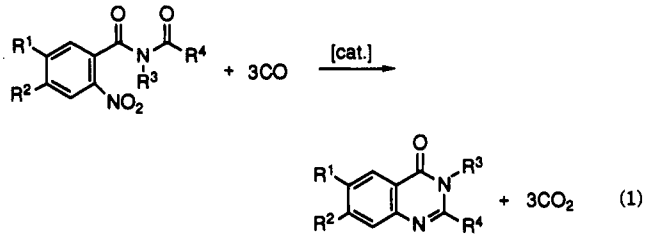
Motohiro Akazome, Teruyuki Kondo, and Yoshihisa Watanabe*

Department of Hydrocarbon Chemistry, Faculty of Engineering, Kyoto University, Sakyo-ku, Kyoto 606-01, Japan

Received September 15, 1992

Summary: Several ruthenium and platinum complexes smoothly catalyze the reductive N-heterocyclization of *N*-(2-nitrobenzoyl)amides under carbon monoxide pressure to afford the corresponding 4(3*H*)-quinazolinone derivatives, including some quinazolinone alkaloids, in good yields.

Transition-metal complexes that can serve as effective tools for the synthesis of various heterocyclic ring systems have been developed in recent years.[1] In our studies of N-heterocyclization reactions catalyzed by transition-metal complexes, and ruthenium complexes in particular, we have sought to develop new, useful synthetic methods.[2] We have recently examined the transition-metal complex-catalyzed reductive N-heterocyclization of nitro compounds which occurs via an active transition-metal nitrene intermediate.[3] Here, we report the first ruthenium-catalyzed syntheses of 4(3*H*)-quinazolinone derivatives by the reductive N-heterocyclization of *N*-(2-nitrobenzoyl)-amides under carbon monoxide pressure (eq 1).



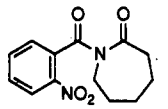
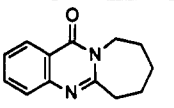
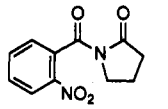
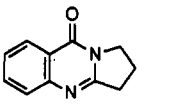
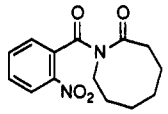
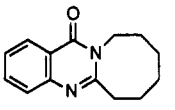
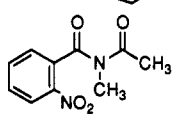
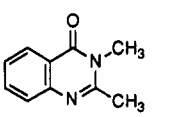
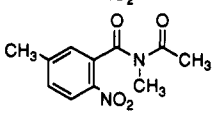
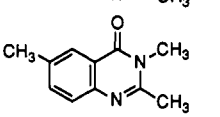
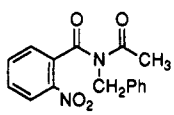
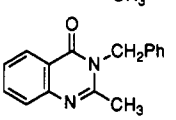
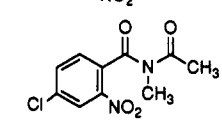
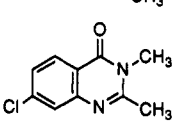
(1)

[cat.] = $Ru_3(CO)_{12}$, $Pt(PPh_3)_4$ etc.

Many of the quinazolinone alkaloids such as tryptanthrine,[4a-c] vasicinone,[4d,e] anisotine,[4f] and rutaecarpine[4g] demonstrate important biological activities. However, there are few examples of catalytic syntheses of these compounds.[5]

Representative examples of the syntheses of 4(3*H*)-quinazolinone derivatives employing $Ru_3(CO)_{12}$ as a catalyst are summarized in Table I. *N*-(2-Nitrobenzoyl)-amides were smoothly transformed into the corresponding 4(3*H*)-quinazolinone derivatives in 68–94% yield.[6] The quinazolinones obtained from this reaction are known to be versatile intermediates in the syntheses of quinazolinone alkaloids. For example, the total synthesis of vasicinone via azacyclopentano[2,1-*b*]-4(3*H*)-quinazolinone, the product in entry 2, was reported by Onaka et al.,[7] and an improved method was later reported by Mori et al.[5]

Table I. Synthesis of 4(3*H*)-Quinazolinone Derivatives from *N*-(2-Nitrobenzoyl)amides in the Presence of $Ru_3(CO)_{12}$ Catalyst[a]

entry	substrate	product	isolated yield (%)
1[b]			88 (92[f])
2			68
3			94
4			93
5			92
6			88
7			77

[a] *N*-(2-Nitrobenzoyl)amides (2.0 mmol), 1,4-dioxane (10 mL), $Ru_3(CO)_{12}$ (0.067 mmol) under CO (40 kg cm^{-2}) at 140 °C for 16 h. [b] At 160 °C. [c] Figure in parentheses is GLC yield.

(1) (a) Colquhoun, H. M.; Holton, J.; Thompson, D. J.; Twigg, M. V. *New Pathyways for Organic Synthesis: Practical Applications of Transition Metals*; Plenum Press: New York, 1984; p 148. (b) McQuillin, F. J.; Parker, D. G.; Stephenson, G. R. *Transition Metal Organometallics for Organic Synthesis*; Cambridge University Press: New York, 1991; p 477. (c) Davidson, J. L.; Preston, P. N. *Adv. Heterocycl. Chem.* **1982**, *30*, 319.

(2) For example, see: (a) Tsuji, Y.; Huh, K.-T.; Watanabe, Y. *J. Org. Chem.* **1987**, *52*, 1673. (b) Tsuji, Y.; Kotachi, S.; Huh, K.-T.; Watanabe, Y. *J. Org. Chem.* **1990**, *55*, 580 and references cited therein. (c) Kondo, T.; Yang, S.; Huh, K.-T.; Kobayashi, M.; Kotachi, S.; Watanabe, Y. *Chem. Lett.* **1991**, 1275.

(3) (a) Akazome, M.; Kondo, T.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1991**, 1466. (b) Akazome, M.; Kondo, T.; Watanabe, Y. *Chem. Lett.* **1992**, 769.

(4) (a) Honda, G.; Tabata, M. *Planta Med.* **1978**, *36*, 85. (b) Honda, G.; Tabata, M.; Tsuda, M. *Planta Med.* **1979**, *37*, 172. (c) Bergman, J.; Lindström, J.-O.; Tilstam, U. *Tetrahedron* **1985**, *41*, 2879. (d) Mehta, D. R.; Naravane, J. S.; Desai, R. M. *J. Org. Chem.* **1963**, *28*, 445. (e) Johne, S.; Gröger, D.; Hesse, M. *Helv. Chim. Acta* **1971**, *54*, 826. (f) Arndt, R. R.; Eggers, S. H.; Jordaan, A. *Tetrahedron* **1967**, *23*, 3521. (g) Asahina, Y.; Manske, R. H. F.; Robinson, R. *J. Chem. Soc.* **1927**, 1708.

(5) Mori, M.; Kobayashi, H.; Kimura, M.; Ban, Y. *Heterocycles* **1985**, *23*, 2803.

(6) **General Procedure.** A mixture of *N*-(2-nitrobenzoyl)amide (2.0 mmol), $Ru_3(CO)_{12}$ (0.067 mmol), and dry 1,4-dioxane (10 mL) was placed in a stainless steel autoclave (Yuasa Giken SUS 316) equipped with a glass linear and a magnetic stirring bar. The unit was sealed and purged of air by pressurization with carbon monoxide to 10 kg cm^{-2} and depressurization to atmospheric pressure. This pressurization–depressurization cycle was repeated twice. The reactor was then again pressurized to 40 kg cm^{-2} with carbon monoxide at room temperature and was heated to 140 °C over 10 min, with stirring. The stirred mixture was held at this temperature for 16 h. The reaction was then quenched by rapid cooling, and the gaseous products were allowed to escape. The resultant brown solution was analyzed by GLC and FT-IR. The products were isolated by Kugelrohr distillation.

(7) Onaka, T. *Tetrahedron Lett.* **1971**, 4387.

0022-3263/93/1958-0310$04.00/0

Scheme I

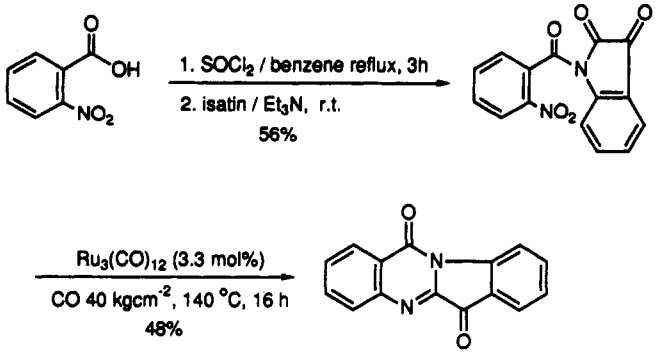


Table II. Catalytic Activities of Several Transition-Metal Complexes for the Reductive N-Heterocyclization of *N*-(2-Nitrobenzoyl)-2-azacycloheptanone[a]

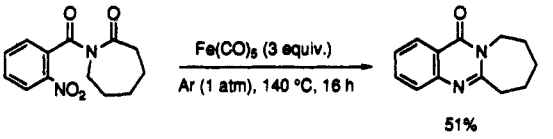
entry	catalyst (mmol)	additive	convn (%)	yield[b] (%)
8	$Ru_3(CO)_{12}$ (0.034)		63	60
9	$Ru(CO)_3(PPh_3)_2$ (0.10)		64	45
10	$RuCl_2(PPh_3)_3$ (0.10)		10	9
11	$RuCl_2(PPh_3)_3$ (0.10)	K_2CO_3[c]	100	67
12	$Pt(PPh_3)_4$ (0.10)		81	76
13	$Pt(CO)_2(PPh_3)_2$ (0.10)		69	65
14	$PtCl_2(PPh_3)_2$ (0.10)		22	17
15	$PtCl_2(PPh_3)_2$ (0.10)	pyridine[d]	65	60
16	$Pd(PPh_3)_4$ (0.10)		34	31
17	$Pd(CO)(PPh_3)_3$ (0.10)		23	19
18	$PdCl_2(PPh_3)_2$ (0.10)	$SnCl_2$[e]	71	13
19	$Fe_3(CO)_{12}$ (0.034)		14	8
20	$Co_2(CO)_8$ (0.050)		9	5
21	$Rh_6(CO)_{16}$ (0.017)		6	4
22	$Mn_2(CO)_{10}$ (0.050)		14	4

[a] *N*-(2-Nitrobenzoyl)-2-azacycloheptanone (2.0 mmol), 1,4-dioxane (10 mL) under CO (20 kg cm^{-2}) at 120 °C for 16 h. [b] Determined by GLC. [c] 3.0 mmol. [d] 1.0 mL (12.4 mmol). [e] 1.0 mmol.

The present reaction can be applied to a facile synthesis of indolo[2,1-*b*]quinazoline-6,12-dione, which is the antibiotic tryptanthrine.[4a-c] As shown in Scheme I, indolo-[2,1-*b*]quinazoline-6,12-dione was obtained in 48% yield by the reductive N-heterocyclization of *N*-(2-nitrobenzoyl)-isatin, which was easily prepared from 2-nitrobenzoic acid and isatin.

The catalytic activities of several transition-metal complexes were examined in the reductive N-heterocyclization of *N*-(2-nitrobenzoyl)-2-azacycloheptanone (Table II). Zero-valent ruthenium and platinum complexes generally showed high catalytic activity (entries 8, 9, 12, and 13). Although the catalytic activities of the divalent $RuCl_2(PPh_3)_3$ and $PtCl_2(PPh_3)_2$ complexes were low (entries 10 and 14), the addition of appropriate bases such as K_2CO_3 or pyridine drastically improved the activity of these complexes (entries 11 and 15). Phosphine ligands did not affect the reaction. However, the catalytic activities of other group VII and VIII metal complexes, including palladium complexes which effectively catalyzed the reductive N-heterocyclization of *N*-(2-nitrobenzylidene)amines to 2*H*-indazoles[3a] and *o*-nitrostyrenes to indoles,[3b] were quite low.

When an excess amount (i.e., 3 equiv) of pentacarbonyliron ($Fe(CO)_5$), instead of a catalytic amount of $Ru_3(CO)_{12}$, was employed in the reaction of *N*-(2-nitrobenzoyl)-2-azacycloheptanone, azacycloheptano[2,1-*b*]-4(3*H*)-quinazolinone was obtained in 51% yield, under an argon atmosphere (eq 2). This result suggests that carbon



(2)

monoxide pressure is not always essential to the reaction, if enough of the transition-metal carbonyl complex is employed.

The present reaction can be understood by assuming a transition-metal nitrene intermediate.[8] First, deoxygenative reduction of the nitro group in *N*-(2-nitrobenzoyl)-amide by carbon monoxide would occur to produce an active nitrene intermediate.[9,10] It is well-known that nucleophilic nitrene complexes react with the carbonyl group of aldehydes and ketones to yield the corresponding imines.[11] For example, Nugent has reported that the reaction of $(Me_3SiO)_2Cr(N^tBu)_2$ with benzaldehyde gives a monooxo complex, $(Me_3SiO)_2CrO(N^tBu)$, together with the Schiff base, benzylidene-*tert*-butylamine.[11b] In the reaction at hand, the *intramolecular metathesis-like* behavior of the generated nitrene complex with a carbonyl group would proceed in a similar manner to give the corresponding quinazolinone and transition-metal–oxo complex. The oxo complex would be reduced to a zero-valent active carbonyl complex by carbon monoxide,[12] completing the catalytic cycle. After the reductive N-heterocyclization of *N*-(2-nitrobenzoyl)-2-azacycloheptanone (entry 1), carbon dioxide was generated and detected in the gas phase in 241% yield, based on the nitro compound. This result can also be explained by the above mechanism.[13]

In conclusion, the transition-metal complex-catalyzed

(8) 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. *Chem. Tech.* **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.

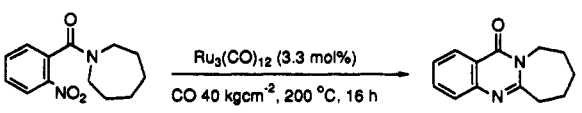
(9) μ_3-Nitrene–ruthenium complexes were isolated from the reaction of $Ru_3(CO)_{12}$ with aromatic nitro compounds. (a) Sappa, E.; Milone, L. *J. Organomet. Chem.* **1973**, *61*, 383. (b) Bhaduri, S.; Gopalkrishnan, K. S.; Sheldrick, G. M.; Clegg, W.; Stalke, D. *J. Chem. Soc., Dalton Trans.* **1983**,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

(10) Although monomeric late-transition-metal nitrene complexes seem to be unstable, Bergman et al. have succeeded in the synthesis of Cp*$Ir N^t$-Bu. (a) Glueck, D. S.; Hollander, F. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 2719. (b) Glueck, D. S.; Wu, J.; Hollander, F. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1991**, *113*, 2041.

(11) (a) Nugent, W. A.; Mayer, J. M. *Metal–Ligand Multiple Bonds*; Wiley-Interscience: New York, 1988. (b) Nugent, W. A. *Inorg. Chem.* **1983**, *22*, 965. (c) Arndtsen, B. A.; Sleiman, H. F.; Chang, A. K.; McElwee-White, L. *J. Am. Chem. Soc.* **1991**, *113*, 4871 and references cited therein.

(12) (a) Herrmann, W. A.; Küsthardt, U.; Schäfer, A.; Herdtweck, E. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 817. (b) Bradford, W.; Nyholm, R. S. *J. Chem. Soc., Chem. Commun.* **1967**, 384.

(13) The reductive N-heterocyclization of *N*-(2-nitrobenzoyl)azacycloheptane, which has no carbonyl group, afforded the corresponding azacycloheptano[2,1-*b*]-4(3*H*)-quinazolinone ($Ru_3(CO)_{12}$ catalyst, 200 °C, 16 h under 40 kg cm^{-2} of CO), although the yield of the product was only 9% (eq 3). This result also suggests the generation of an active nitrene intermediate which can insert into a saturated C–H bond[14] and excludes that the reaction proceeds via the corresponding *N*-(2-aminobenzoyl)-amide.



(3)

(14) Smith, P. A. S. In *Nitrenes*; Lwowski, W., Ed.; Interscience Publishers: New York, 1970; Chapter 4, p 99.

reductive N-heterocyclization reaction provides a useful method for the synthesis of 4(3*H*)-quinazolinone derivatives from *N*-(2-nitrobenzoyl)amides. Work is now in progress to provide definitive mechanistic information and to apply this reductive N-heterocyclization to the construction of additional heterocyclic ring systems.

Supplementary Material Available: Characterization data for all products and a general experimental procedure (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.