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NEW ROUTES TO NITROGEN HETEROCYCLES THROUGH INTRAMOLECULAR AMIDOCARBONYLATION OF ALKENAMIDES CATALYZED BY RHODIUM COMPLEXES

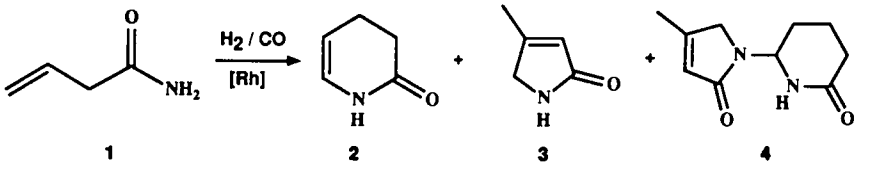
Iwao Ojima* and Anna Korda
Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11794

Summary: *Intramolecular amidocarbonylation of 3-butenamide catalyzed by a rhodium complex with excess PPh_3 gives 3,4-dihydro-2-pyridone selectively, whereas the same reaction using $P(OPh)_3$ affords a unique heterodimer in excellent yield. The reaction of 4-pentenamide gives 4-methyl-3,4-dihydro-2-pyridone exclusively regardless of the structure of rhodium catalysts.*

Dihydro-2-pyridone skeleton is one of the important nitrogen heterocycles for pharmaceutical and agrochemical agents.[1] Simple dihydro-2-pyridones have been synthesized by the direct reaction of 2,4-pentadienoic acid or sorbic acid with ammonia[2] and by the sodium borohydride reduction of glutarimide.[3] The former reaction gives a mixture of 3,6-dihydro- and 5,6-dihydro-2-pyridones, while the latter yields 3,4-dihydro-2-pyridones selectively.

We describe here new and convenient routes to 3,4-dihydro-2-pyridones through intramolecular amidocarbonylation[4] of alkenamides as well as a novel coupling reaction giving 6-(4-methyl-3-pyrrolidin-2-on-1-yl)-2-piperidone.

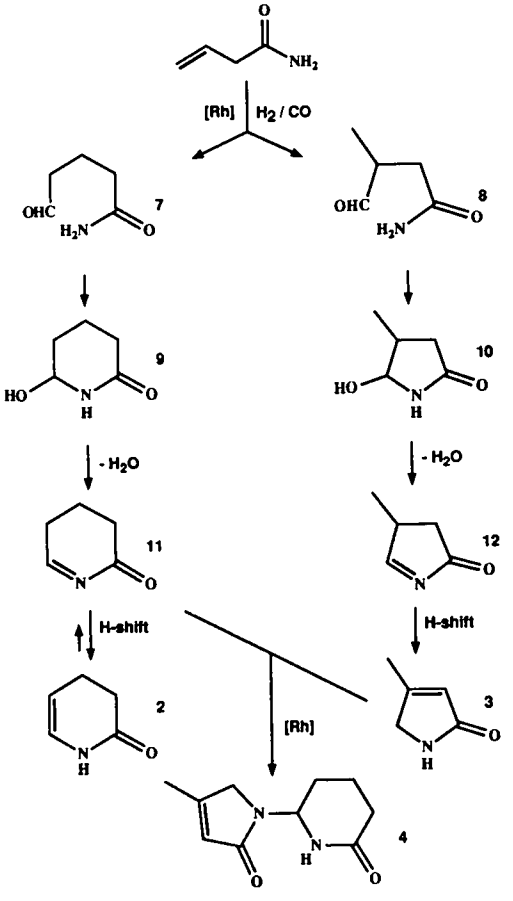
First, the intramolecular amidocarbonylation of 3-butenamide (**1**) was carried out using typical rhodium catalysts for hydroformylation, i.e., $RhCl(PPh_3)_3$, $RhCl(CO)(PPh_3)_2$, and $Rh_4(CO)_{12}$, at 80-100°C and 1,200 psi (CO/H_2 = 3/1 or 1/1) (eq. 1). Results are shown in Table 1.



1 **2** **3** **4** (1)

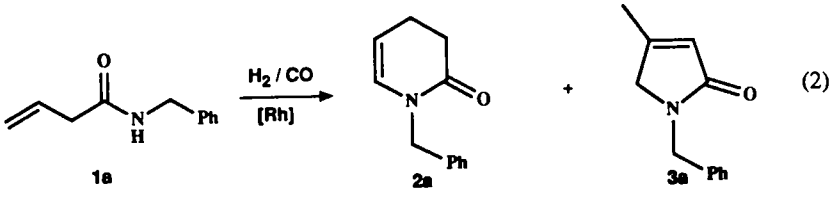
As Table 1 shows, the reaction under those conditions gave a mixture of 3,4-dihydro-2-pyridone (**2**), 4-methyl-3-pyrrolin-2-one (**3**), and a heterodimer, 6-(4-methyl-3-pyrrolin-2-on-1-yl)-2-piperidone (**4**).[5] It is quite reasonable to assume that **2** and **3** are formed via 6-formylpentanamide (**7**) and 5-formylpentanamide (**8**), respectively, whereas **4** is yielded via the crossed coupling of **2** (via **11**) and **3** under the reaction conditions, as shown in Scheme 1. *It should be noted that only the crossed-coupling product, heterodimer (4), was obtained and no homocoupling of 2 nor 3 was observed at all.*

Scheme 1



In order to obtain **2**-**4** selectively, we examined the effects of phosphine ligands on the regioselectivity as well as monomer/dimer selectivity of the reaction. As Table 1 shows (Entry 3), the addition of 20 equivalents of triphenylphosphine to $RhCl(PPh_3)_3$ remarkably improved the selectivity for the formation of **2** (92%) and no heterodimer (**4**) was formed. On the order hand, when 10 equivalents of triphenylphosphite were employed instead of triphenylphosphine for $RhCl(PPh_3)_3$, the heterodimer (**4**) was produced with excellent selectivity (94%) in 90% yield. The heterodimer (**4**) may serve as a useful intermediate for the synthesis of tricyclic or tetracyclic nitrogen heterocycles. Reaction conditions which afford **3** selectively have not been found so far.

Next, we employed N-benzyl-3-butenamide (**1a**) as the substrate (eq. 2).[6] It was found that the N-benzylation of **1** favors the formation of a 2-pyrrolinone (**3a**) to some extent, viz., the reaction catalyzed by $RhCl(PPh_3)_3$ at 1,200 psi (CO/H_2 = 1) gave **3a** as the major product, e.g., **3a/2a** = 2 (70% yield) at 100°C; **3a/2a** = 3 (80% yield) at 120°C.[5] The results make a contrast with those for **1** in which the 2-pyrrolinone (**3**) is the minor product. However, the addition of 20 equivalents of triphenylphosphine to $RhCl(CO)(PPh_3)_2$[7] gave **2a** with 91% selectivity in 98% yield like the case of **1**. Because of the N-protection, no dimer formation was observed with this substrate.



Finally, the reaction of 4-pentenamide (**5**) was examined in a similar manner (eq. 3). Results are shown in Table 2.

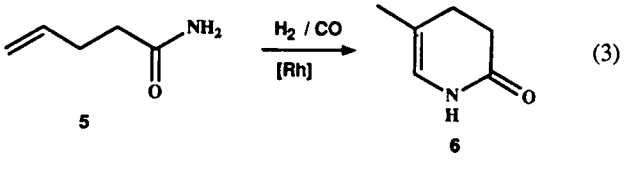


Table 1. Intramolecular amidocarbonylation of 3-butenamide (**1**)[a]

Entry	Catalyst	CO (psi)	H_2 (psi)	Temp. (°C)	Time (h)	Yield[b] (%)	Product ratio (%)[c] **2**	**3**	**4**
1	$RhCl(PPh_3)_3$	900	300	80	18	92	13	9	78
2	$RhCl(PPh_3)_3$/10 PPh_3	900	300	80	40	99	57	17	26
3	$RhCl(PPh_3)_3$/20 PPh_3	900	300	80	40	100	**92**	8	---
4	$RhCl(CO)(PPh_3)_2$	600	600	100	18	96	18	10	72
5	$RhCl(CO)(PPh_3)_2$/10 PPh_3	600	600	100	40	99	47	6	47
6	$RhCl(CO)(PPh_3)_2$/20 PPh_3	600	600	100	40	98	74	9	17
7	$Rh_4(CO)_{12}$	600	600	80	18	98	25	22	53
8	$RhCl(PPh_3)_3$/10 $P(OPh)_3$	900	300	80	40	90	3	3	**94**

[a] All reactions were run with 3-butenamide (1) (1.50 mmol) and a rhodium catalyst (0.015 mmol) in THF (3.6 mL) in a stainless steel autoclave (300 mL) using a Pyrex reaction vessel (50 mL) with magnetic stirring. Conversion was 100% for all cases. Products were isolated by column chromatography on neutral alumina and identified by ^1H and ^{13}C NMRs, IR, and Mass spectroscopies. [b] Determined by GLC analysis. [c] Determined by GLC and ^1H NMR analyses.

Table 2. Synthesis of 4-methyl-3,4-dihydro-2-pyridone (**6**) through intramolecular amidocarbonylation of 4-pentenamide (**5**)[a]

Entry	Catalyst	CO (psi)	H_2 (psi)	Temp. (°C)	Time (h)	Yield[b] (%)
1	$RhCl(PPh_3)_3$	600	600	100	18	91
2	$RhCl(CO)(PPh_3)_2$	600	600	100	18	89
3	$HRh(CO)(PPh_3)_3$	600	600	100	18	88
4	$Rh_4(CO)_{12}$	600	600	100	18	92

[a] All reactions were run with 1.50 mmol of 4-pentenamide and 0.015 mmol of a rhodium catalyst in THF (3.6 mL) in an autoclave (300 mL) using a Pyrex reaction vessel (50 mL). The product, **6**, was isolated by column chromatography on silica gel. [b] Isolated yield.

As Table 2 shows, the reaction catalyzed by several rhodium complexes gave 4-methyl-3,4-dihydro-2-pyridone (**6**) as the sole product in excellent yield (88-92%). Although the formation of a seven-membered ring lactam is conceptually possible, such a product was not detected at all even when 20 equivalents of triphenylphosphine to $RhCl(PPh_3)_3$ were employed as additive. The result clearly indicates that a "chelation control" is operative in this reaction.

The result also strongly suggests that a similar "chelation control" is operating in the reactions of **1** and **1a** as well. Thus, the effects of a large excess of triphenylphosphine to the rhodium catalysts cannot be accommodated by the blocking (or disruption) of the amide-directed "chelation control", but can be interpreted as the regioselective hydroformylation of **1** (or **1a**) with the amide chelation intact, viz., it is clearly indicated that the coordination of alkenamide to the rhodium catalysts is much stronger than that of triphenylphosphine.[8]

Further mechanistic investigation as well as application of these reactions to the synthesis of a variety of nitrogen heterocycles are actively underway.

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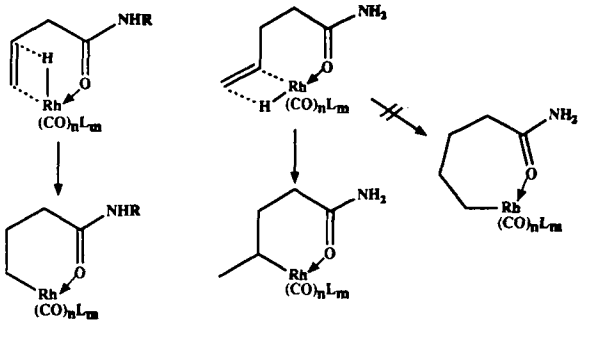
References and Notes

1. e.g., (a) Jones, R. A.; Bean, G. P. *"The Chemistry of Pyrroles"*; Academic Press: London, **1977**; pp 209-238. (b) Coutts, R. T.; Casy, A. F. *"Pyridines and Reduced Pyridines of Pharmacological Interests"*, In *"Heterocyclic Compounds Pyridine and Its Derivatives"*, Abramovitch (Ed.); John Wiley Interscience: New York, **1975**; pp 445-524.
2. Kheddis, B.; Bahibah, D.; Hamdi, M.; Périé, J.-J. *Bull. Soc. Chim. France*, **1981**, 135.
3. Hubert, J. C.; Wijnberg, J. B. P. A.; Nico Speckamp, W. N. *Tetrahedron*, **1975**, *31*, 1437.
4. (a) For intramolecular amidocarbonylation of N-allyl- and N-methallylamides giving N-acylpyrrolidines, see Ojima, I.; Zhang, Z. *J. Org. Chem.*, **1988**, *53*, 4422. (b) For original $Co_2(CO)_8$-catalyzed amidocarbonylation of aldehydes, see Wakamatsu, M.; Uda, J.; Yamazaki, N. *Chem. Commun.*, **1971**, 1540. (c) For applications of $Co_2(CO)_8$-catalyzed amidocarbonylation, see, e.g., Izawa, K.; Nishi, S.; Asada, S. *J. Mol. Catal.*, **1987**, *41*, 135; K. Izawa *J. Syn. Org. Chem., Japan*, **1988**, *46*, 218. (d) For other applications of amidocarbonylation, see Ojima, I. *Chem. Rev.*, **1988**, *88*, 1011 and references cited therein.
5. **4**: mp 151-152°C; ^{1}H NMR ($CDCl_3$) δ 1.7-2.1 (m, 2H), 2.2-2.5 (m, 4H), 2.10 (s, 3H), 3.86 (d, J = 18.5 Hz, 1H), 3.98 (d, J = 18.5 Hz, 1H), 5.69 (t, J = 4.2 Hz, 1H), 5.86 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.45, 18.89, 27.11, 31.12, 50.89, 59.55, 122.29, 156.81, 172.19, 172.30; IR (KBr disk) 3230 (ν_{NH}), 1682 ($\nu_{C=O}$) cm^{-1}.
6. The amidocarbonylation of **1a** catalyzed by $Co_2(CO)_8$ at 100°C and 1,470 psi (CO/H_2 = 1) was reported to give 3-(N-benzylcarbamoyl)-2-methylpropanoic acid in 69% yield, viz., no formation of nitrogen heterocycles was observed. See Nishi, S.; Asada, S.; Izawa, K. *31st Symposium on Organometallic Chemistry, Japan*, Oct. 30-31, Tsukuba, Japan, **1984**; Abstract B202.
7. The reaction catalyzed by $RhCl(PPh_3)_3$/20 PPh_3 gave **2'** with 78% selectivity in 79% yield. Thus, $RhCl(CO)(PPh_3)_3$/20 PPh_3 turns out to be much better catalyst.
8. We can assume the following six-membered ring chelate alkyl-Rh complexes as major (for **1** and **1a**) or exclusive (for **5**) key intermediates in the first step of intramolecular amidocarbonylation. Similar intermediates were discussed in a cobalt-catalyzed reaction of N-alkenylbenzamides.[4c]



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