JOC*Note*

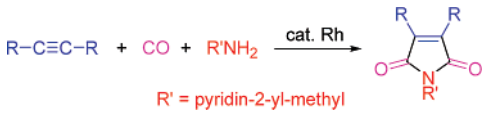
A Chelation-Assisted Transformation: Synthesis of Maleimides by the Rh-Catalyzed Carbonylation of Alkynes with Pyridin-2-ylmethylamine

Satoshi Inoue, Yoshiya Fukumoto, and Naoto Chatani*

Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

chatani@chem.eng.osaka-u.ac.jp

Received May 20, 2007

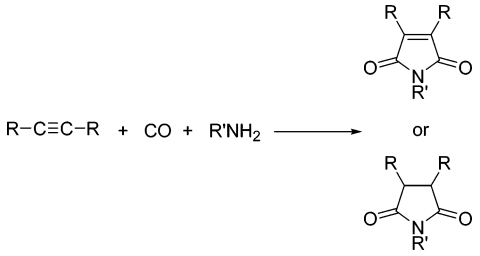


The reaction of alkynes **1** with CO and pyridin-2-ylmethylamine (**2**) in the presence of $Rh_4(CO)_{12}/P(OEt)_3$ results in the incorporation of two molecules of CO leading to maleimide derivatives **3**. The coordination of the pyridine nitrogen in **2** to a rhodium center is essential for the reaction to proceed.

Carbonylation is a useful method for the preparation of various carbonyl compounds in both industrial and laboratorial settings.[1] A variety of cyclic and acyclic carbonyl compounds, such as aldehydes, carboxylic acids, esters, amides, lactones, and lactams, have been prepared by transition metal-promoted carbonylation reactions. However, there are few methods available for the preparation of imides by the utilization of CO. Falbe et al. reports that imides were obtained by the $Co_2(CO)_8$-catalyzed carbonylation of unsaturated amides under vigorous conditions.[2] The reaction of alkynes with molecules of CO and amines would be a straightforward and attractive method for the preparation of five-membered imides because of the availability of the starting materials and of the atom-economy (Scheme 1). However, this transformation has not appeared in the literature, to the best of our knowledge, although carbonylation of alkynes with amines leading to α,β-unsaturated amides is well-known.[3,4]

A chelation-assisted transformation is recognized as one of the most reliable methodologies not only for controlling regio- and stereoselectivity of reactions and accelerating reactions, but also for leading to new reactions.[5−8] During the development of new chelation-assisted catalytic reactions, it was found that the reaction of internal alkynes with CO and pyridin-2-ylmethanol in the presence of a rhodium complex results in a double-hydroesterification to give 1,4-dicarboxylate esters.[8] The use of simple alcohols, such as methanol, ethanol, and benzyl alcohol, did not give these double-hydroesterification products, but instead well-known monohydroesterification reactions took place. It was found that the monohydroesterification products do not appear to be intermediates in the formation of double-hydroesterification products, showing that the presence of the pyridine ring in alcohols has a significant effect on the reaction course. The presented study investigates the Rh-catalyzed reaction of alkynes **1** with CO and pyridin-2-ylmethylamine (**2**) leading to maleimides **3**. The coordination of the sp^2 nitrogen in **2** is an essential step for the reaction to proceed.

SCHEME 1. Imide Synthesis from Alkynes, CO, and Amines



The reaction of 4-octyne (**1a**, 2 mmol) with pyridin-2-ylmethylamine (**2**, 1 mmol) under CO (3 atm) in toluene (1

(1) For reviews on carbonylation reactions, see: Mullen, A. In *New Syntheses with Carbon Monoxide*; Falbe, J., Ed.; Springer-Verlag: Berlin, Germany, 1980; pp 242−308. Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation. Direct Synthesis of Carbonyl Compounds*; Plenum Press: New York, 1991. Ali, B. E.; Alper, H. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wil1ey-VCH: Weinheim, Germany, 1998: pp 49−67. Kiss, G. *Chem. Rev.* **2001**, *101*, 3435−3456. Chiusoli, G.; Costa, M. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; Vol. 2, pp 2595−2621. Beller, M. *Catalytic Carbonylation Reactions* (*Topics in Organometallic Chemistry*); Springer-Verlag: Berlin, Germany, 2006.

(2) Falbe, J.; Korte, F. *Chem. Ber.* **1962**, *95*, 2680−2687.

(3) For a recent paper on the Pd-catalyzed reaction of alkynes with CO and amines leading to α,β-unsaturated amides, see: Li, Y.; Alper, H.; Yu, Z. *Org. Lett.* **2006**, *8*, 5199−5201.

(4) For a paper on the $Rh_4(CO)_{12}$-catalyzed reaction of alkynes with CO and amines leading to α,β-unsaturated amides, see: Joh, T.; Doyama, K.; Onitsuka, K.; Shiohara, T.; Takahashi, S. *Organometallics* **1991**, *10*, 2493−2498.

(5) For our papers on chelation-assisted carbonylation at C−H bonds, see: Chatani, N.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **1996**, *118*, 493−494. Chatani, N.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **1997**, *62*, 2604−2610. Fukuyama, T.; Chatani, N.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **1997**, *62*, 5647−5650. Ishii, Y.; Chatani, N.; Kakiuchi, F.; Murai, S. *Organometallics* **1997**, *16*, 3615−3622. Ishii, Y.; Chatani, N.; Kakiuchi, F.; Murai, S. *Tetrahedron Lett.* **1997**, *38*, 7565−7568. Fukuyama, T.; Chatani, N.; Tatsumi, J.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **1998**, *120*, 11522−11523. Chatani, N.; Ishii, Y.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **1998**, *63*, 5129−5136. Ie, Y.; Chatani, N.; Ogo, T.; Marshall, D. R.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2000**, 65, 1475−1488. Chatani, N.; Fukuyama, T.; Tatamidani, H.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2000**, *65*, 4039−4047. Chatani, N.; Asaumi, T.; Ikeda, T.; Yorimitsu, S.; Ishii, Y.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2000**, *122*, 12882−12883. Chatani, N.; Yorimitsu, S.; Asaumi, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2002**, *67*, 7557−7560. Asaumi, T.; Chatani, N.; Matsuo, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2003**, *68*, 7538−7540. Asaumi, T.; Matsuo, T.; Fukuyama, T.; Ie, Y.; Kakiuchi, F.; Chatani, N. *J. Org. Chem.* **2004**, *69*, 4433−4440. Chatani, N.; Uemura, T.; Asaumi, T.; Ie, Y.; Kakiuchi, F.; Murai, S. *Can. J. Chem.* **2005**, *83*, 755−763. Imoto, S.; Uemura, T.; Kakiuchi, F.; Chatani, N. *Synlett* **2007**, 170−172.

(6) For recent selected reviews on chelation-assisted transformations, see: Itami, K.; Yoshida, J. *Synlett* **2006**, 157−180. Godula, K.; Sames, D. *Science* **2006**, *312*, 67−72. Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q.-P.; Lazareva, A. *Synlett* **2006**, 3382−3388. Yu, J.-Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041−4047. Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439−2463. Jun, C.-H.; Jo, E.-A.; Park, J.-W. *Eur. J. Org. Chem.* **2007**, 1869−1881.

(7) Yokota, K.; Tatamidani, H.; Fukumoto, Y.; Chatani, N. *Org. Lett.* **2003**, *5*, 4329−4331.

(8) Inoue, S.; Yokota, K.; Tatamidani, H.; Fukumoto, Y.; Chatani, N. *Org. Lett.* **2006**, *8*, 2519−2522.

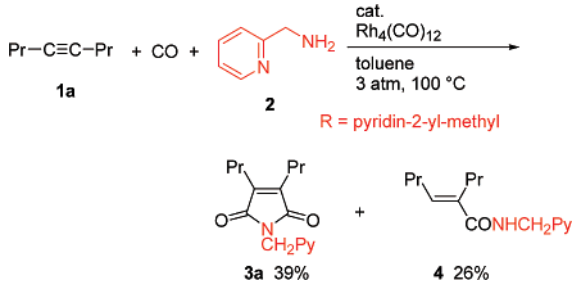
10.1021/jo071029p CCC: $37.00
Published on Web 07/27/2007

TABLE 1. Effect of Additives[a]

entry	additive	temp, °C	yields[b] % 3a	4
1	PPh_3	100	22	36
2	PPh_3	120	41	25
3	$P(4\text{-}CF_3C_6H_4)_3$	120	6	40
4	$P(OEt)_3$	100	69	12
5	$P(OEt)_3$[c]	100	44	16
6	$P(OEt)_3$	80	62	13
7	$P(OEt)_3$	120	53	26
8	$P(OMe)_3$	100	53	20
9	$P(OPr^i)_3$	100	47	17
10	$P(OPh)_3$	120	26	52
11	$O{=}P(OEt)_3$	120	42	30

[a] Reaction conditions: alkyne **1** (2 mmol), 2-pyridinylmethylamine **2** (1 mmol), $Rh_4(CO)_{12}$ (0.02 mmol), $P(OEt)_3$ (0.08 mmol), in toluene (1 mL) under CO (3 atm) at 100 °C for 20 h. [b] Isolated yield by column chromatography. [c] $P(OEt)_3$ (0.16 mmol) was used.

SCHEME 2. The Reaction of 4-Octyne (1a) with CO and Pyridin-2-ylmethylamine (2)



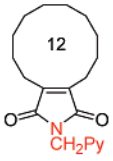
mL) at 100 °C in the presence of $Rh_4(CO)_{12}$ (0.02 mmol) for 20 h gave 3,4-dipropyl-1-(pyridin-2-ylmethyl)pyrrole-2,5-dione (**3a**) in 39% isolated yield and 2-propylhex-2-enoic acid (pyridin-2-ylmethyl)amide (**4**) in 26% yield (Scheme 2). An increase in the reaction temperatures increased the yield of **3a** (17% at 80 °C; 39% at 100 °C; 42% at 120 °C). However, no reaction took place at 130 °C, because $Rh_4(CO)_{12}$ was decomposed at 130 °C. Actually, the color of the reaction mixture was reddish brown when the reaction was carried out at 120 °C or less, but the color was black at 130 °C. We next examined the effect of additives on the selectivity (Table 1). It was found that the addition of phosphite improved the yield of **3a**. The use of $P(OEt)_3$ (0.08 mmol) as an additive improved the yield of **3a** to 69% (entry 4). No significant improvement was observed, but the use of $P(4\text{-}CF_3C_6H_4)_3$ and $P(OPh)_3$ led to a selective formation of **4** (entries 3 and 10).

In contrast to **2**, the use of benzylamine did not give the corresponding maleimide **3a**. When the reaction of **1a** (2 mmol) was carried out with benzylamine (1 mmol), α,β-unsaturated amide **5** and succinamide **6** were obtained in 39% and 20% yields, respectively (Scheme 3). This result shows that the conversion of alkynes to maleimide **3** is achieved only when **2** is used. Takahashi also found that the reaction of diphenylacetylene with CO (100 atm) and amines at 100 °C in the presence of $Rh_4(CO)_{12}$ gives α,β-unsaturated amides.[4]

The results of the reaction of various alkynes are shown in Table 2. Both aliphatic and aromatic internal alkynes gave the corresponding maleimides in good yield. On the other hand, a terminal alkyne, such as 1-octyne, gave the corresponding maleimide **3g** in low yield.

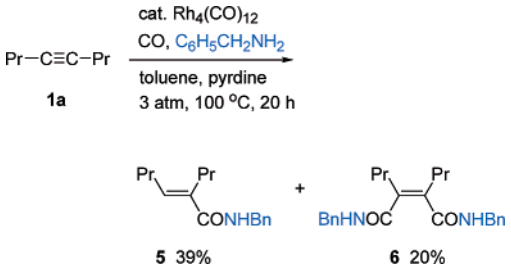
To gain an insight into the reaction mechanism, control experiments were performed (Scheme 4). The exposure of α,β-

TABLE 2. The $Rh_4(CO)_{12}$-Catalyzed Carbonylation of Alkynes with CO and Pyridin-2-ylmethylamine (2)[a]

entry	alkyne	product	yield[b]
1	C_5H_{11}−C≡C−Me **1b**	 **3b**	51%
2	Ph−C≡C−Me **1c**	 **3c**	44%
3	Ph−C≡C−Bu **1d**	 **3d**	42%
4	Ph−C≡C−Ph **1e**	 **3e**	52%
5	 **1f**	 **3f**	51%
6	C_6H_{13}−C≡C−H **1g**	 **3g**	18%[c]

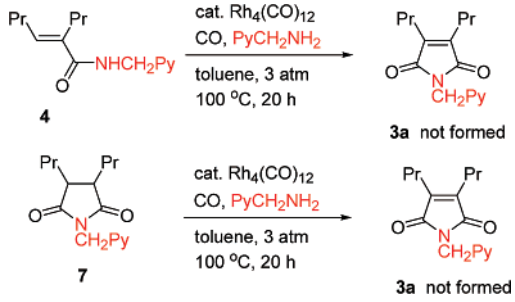
[a] Reaction conditions: alkyne **1** (2 mmol), 2-pyridinylmethylamine **2** (1 mmol), $Rh_4(CO)_{12}$ (0.02 mmol), $P(OEt)_3$ (0.08 mmol), in toluene (1 mL) under CO (3 atm) at 100 °C for 20 h. [b] Isolated yield by column chromatography. [c] No phosphite was added.

SCHEME 3. The Reaction of 4-Octyne (1a) with CO and Benzylamine

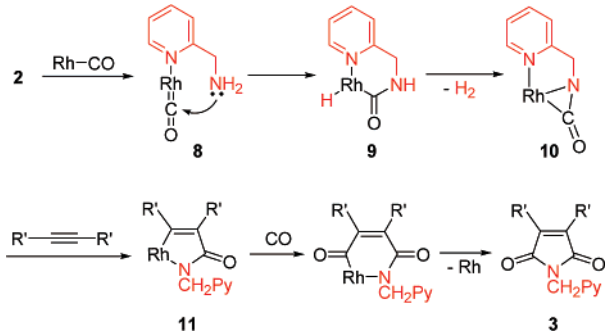


unsaturated amide **4** (1 mmol), under identical conditions, did not result in the formation of **3a**, but **4** was recovered in 96% yield. If the reaction had proceeded via the mechanism similar to that of pyridin-2-ylmethanol,[8] a saturated imide **7** would have been obtained. When **7** was exposed under the reaction conditions, **3a** was not formed, but **7** was recovered in 98% yield. Dehydrogenation of **7** did not occur to give **3a** under the reaction conditions. According to these results, **4** and **7** do not appear to be intermediates in the formation of **3a**.

SCHEME 4. Control Experiments



SCHEME 5. A Proposed Reaction Mechanism



A proposed reaction mechanism is shown in Scheme 5. The coordination of the pyridine nitrogen in **2** to the rhodium center facilitates the intramolecular attack of the amine on the coordinated carbon monoxide to give a rhodium hydride species **9**. The elimination of H_2 gives η^2-isocyanate−rhodium complex **10**,[9] which reacts with an alkyne to give **11**. The insertion of CO in **11** was followed by reductive elimination to afford maleimide **3** and the rhodium catalyst is regenerated.[11] The coordination of **2** to the rhodium center is required to form an active species such as **10**, although there is no experimental evidence. Kondo et al. reported that the $Ru_3(CO)_{12}$-catalyzed carbonylation of alkynes with isocyanates affords maleimides and a complex related to **11**, which is proposed as a key intermediate.[11]

In summary, the reaction described here represents a new synthesis of maleimides from the reaction of alkynes, CO, and pyridin-2-ylmethylamine (**2**). To the best of our knowledge, this is the first example of the carbonylation of alkynes with amines to maleimide derivatives. The coordination of the pyridine nitrogen in **2** to a rhodium center is crucial for the reaction to proceed.

Experimental Section

Typical Procedure for Carbonylation of Alkynes with Pyridin-2-ylmethylamine (2). $Rh_4(CO)_{12}$ (15 mg, 0.02 mmol), $P(OEt)_3$ (13 mg, 0.08 mmol), pyridin-2-ylmethylamine (**2**, 108 mg, 1.00 mmol), 4-octyne (220 mg, 2.00 mmol), and toluene (1 mL) were placed in a 50-mL stainless steel autoclave under N_2. The system was flushed with 10 atm of carbon monoxide three times. Finally, it was pressurized to 3 atm. The autoclave was heated in an oil bath at 100 °C for 20 h, followed by cooling to rt. Then CO was released. The contents were transferred to a round-bottom flask with EtOAc, and the volatiles were removed in vacuo. The residue was subjected to flash column chromatography on silica gel (eluent: hexane/EtOAc = 9/1→0/1) to give 3,4-dipropyl-1-(pyridin-2-ylmethyl)pyrrole-2,5-dione (**3a**) (188 mg, 69% yield based on **2**) as a pale yellow oil and 2-propylhex-2-enoic acid (pyridin-2-ylmethyl)amide (**4**) (29 mg, 12% yield).

3,4-Dipropyl-1-(pyridin-2-ylmethyl)-1*H*-pyrrole-2,5-dione (3a): Pale yellow oil. R_f 0.48 (hexane/EtOAc = 1/1). ^{1}H NMR ($CDCl_3$) δ 0.97 (t, J = 7.3 Hz, 6H), 1.60 (m, J = 7.3 Hz, 4H), 2.40 (t, J = 7.6 Hz, 4H), 4.81 (s, 2H), 7.13−7.18 (c, 2H), 7.63 (dt, J = 1.6, 7.8 Hz, 1H), 8.52 (d, J = 4.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 14.21, 22.04, 25.84, 42.89, 121.18, 122.25, 136.65, 141.18, 149.24, 155.64, 171.65. IR (neat) 1768, 1708, 1594, 1430, 1402, 1355, 1110, 754. MS, *m*/*z* (rel intensity, %) 272 (M^+, 18), 258 (7), 257 (39), 244 (19), 243 (100), 215 (13), 107 (10), 93 (39), 92 (63), 81 (15), 80 (8), 79 (22). Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29; O, 11.75. Found: C, 70.28; H, 7.38; N, 10.15.

Acknowledgment. This work was partially supported by The Ministry of Education, Science, Sport, and Culture, Japan. N.C. acknowledges the Sumitomo Foundation for their financial support.

Supporting Information Available: Experimental details and the characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO071029P

(9) For papers on η^2-isocyanate complexes, see: Monica, G. L.; Cenini, S.; Freni, M. *J. Organomet. Chem.* **1974**, *76*, 355−365. Drapier, J.; Hoornaerts, M. T.; Hubert, A. J.; Teyssie, P. *J. Mol. Catal.* **1981**, *11*, 53−68.

(10) Isocyanates are well-known to participate in cycloaddition reactions as two-atom components. For recent papers, see: Yamamoto, Y.; Kinpara, K.; Saigoku, T.; Takagishi, H.; Okuda, S.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2005**, *127*, 605−613; Boñaga, L. V. R.; Zhang, H.-C.; Moretto, A. F.; ye, H.; Gauthier, D. A.; Li, J.; leo, G. C.; Maryanoff, B. E. *J. Am. Chem. Soc.* **2005**, *127*, 3473−3474. Tanaka, K.; Hagimura, Y.; Hirano, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 2734−2737. Yu, R. T.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 14816−14817.

(11) Kondo, T.; Momura, M.; Ura, Y.; Wada, K.; Mitsudo, T. *J. Am. Chem. Soc.* **2006**, *128*, 14816−14817.