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Rhodium Complex-Catalyzed Reaction of Isonitriles with Carbonyl Compounds: Catalytic Synthesis of Pyrroles

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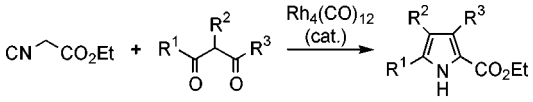
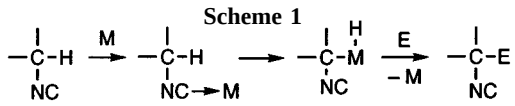
ABSTRACT



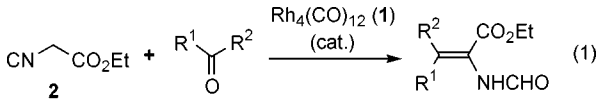
Low-valent rhodium complexes are efficient catalysts for the activation of α-C–H bond of isonitriles. Addition of isonitriles to carbonyl compounds proceeds under mild and neutral conditions to give the corresponding α,β-unsaturated formamides. Catalytic synthesis of pyrroles can be performed by cyclocondensation of isonitriles with 1,3-dicarbonyl compounds.

We have been investigating transition-metal-catalyzed C−H bond activations induced by α-heteroatom effects.[1] Upon treatment with low-valent transition-metal complexes, activations of α-C−H bond of amines[2] and nitriles[3,4] can be performed efficiently. In the case of nitriles, the activated intermediates can be trapped with electrophiles to form carbon−carbon bonds at the α-position of nitriles under neutral and mild reaction conditions. This concept led us to find rhodium-catalyzed activation of C−H bonds α to isonitriles which have strong coordination ability toward metals (Scheme 1). Capture of the α-metalated intermediate

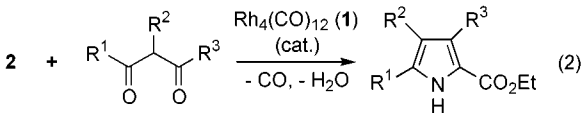
Scheme 1



thus formed with electrophiles such as carbonyl compounds provides a highly useful method for the formation of a carbon−carbon bond at the α-position of isonitriles under neutral conditions. Herein, we wish to report that rhodium-catalyzed addition of isonitriles to carbonyl compounds occurs to give the corresponding α,β-unsaturated formamides (eq 1) and also the application of this method for catalytic synthesis of pyrroles from 1,3-dicarbonyl compounds and isonitriles (eq 2).



(1)



(2)

In the presence of 5 mol % of rhodium carbonyl complex, $Rh_4(CO)_{12}$ (**1**), the reaction of isonitriles such as ethyl isocyanoacetate (**2**) with ketones took place to give the corresponding α,β-unsaturated formamides, which are con-

(1) For a review on C−H activations by the α-heteroatom effect, see: Murahashi, S.-I.; Naota, T. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1805.

(2) (a) Murahashi, S.-I.; Hirano, T.; Yano, T. *J. Am. Chem. Soc.* **1978**, *100*, 348. (b) Murahashi, S.-I.; Watanabe, T. *J. Am. Chem. Soc.* **1979**, *101*, 7429.

(3) For reviews on C−H activations of nitriles, see: (a) Murahashi, S.-I.; Takaya, H. *Acc. Chem. Res.* **2000**, *33*, 225. (b) Naota, T.; Murahashi, S.-I.; Takaya, H. *Chem. Rev.* **1998**, *98*, 2599.

(4) (a) Naota, T.; Taki, H.; Mizuno, M.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1989**, *111*, 5954. (b) Murahashi, S.-I.; Naota, T.; Taki, H.; Mizuno, M.; Takaya, H.; Komiya, S.; Mizuho, Y.; Oyasato, N.; Hiraoka, M.; Hirano, M.; Fukuoka, A. *J. Am. Chem. Soc.* **1995**, *117*, 12436. (c) Takaya, H.; Naota, T.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1998**, *120*, 4244.

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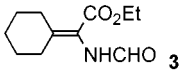
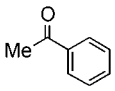
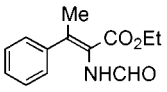
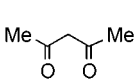
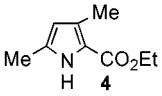
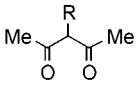
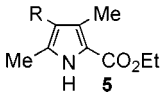
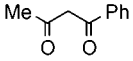
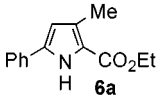
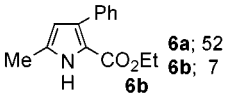
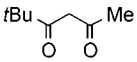
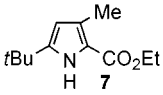
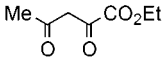
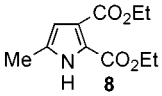
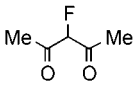
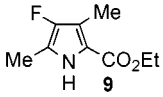
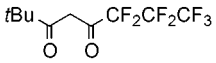
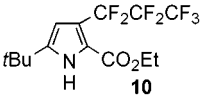
sidered to be important precursors of *N*-formylamino acid ethyl esters.[5] Representative results of the formation of α,β-unsaturated formamides are shown in Table 1 (entries 1 and 2). The reaction of **2** with ketones induced by stoichiometric amounts of strong bases such as butyllithium has been reported to give the corresponding formamides.[6] It is noteworthy that the products derived from α-C−H activation of carbonyl compounds are not formed, although carbonyl compounds generally show lower pK_a values than those of the corresponding isonitriles.[7] This result suggests that the C−H activation occurs chemoselectively at the α-position of isonitriles because of their stronger coordination ability to metals.[8] Rhodium carbonyl complex $Rh_4(CO)_{12}$ (**1**) has proven to be the best catalyst among the catalysts examined. Mononuclear rhodium hydride complexes such as $RhH(CO)(PPh_3)_3$ and $RhH(PPh_3)_4$ are also good catalysts and gave the formamide **3** in 77% and 70% yields, respectively.

Table 1. Rhodium-Catalyzed Reactions of Ethyl Isocyanoacetate (**2**) with Carbonyl Compounds[a]

entry	carbonyl compound	product	yield (%)[b]
1		 **3**	85
2			78
3		 **4**	84[c]
4		 **5**	R = Me **5a**; 68 = -CH_2CH_2CN **5b**; 52
5		 **6a**  **6b**	**6a**; 52 **6b**; 7
6		 **7**	65
7		 **8**	76
8		 **9**	40
9		 **10**	70

[a] A mixture of 1,3-dicarbonyl compound (2.0 mmol), ethyl isocyanoacetate (**2**) (1.0 mmol), and $Rh_4(CO)_{12}$ (**1**) (0.0075 mmol, 3 mol% based on Rh) in dry toluene (0.5 mL) was stirred under an argon atmosphere for 4 h at 80 °C. [b] Isolated yield based on **2**. [c] Reaction temperature, 25 °C.

Importantly, the present reaction can be applied to the catalytic synthesis of pyrroles upon treatment with 1,3-dicarbonyl compounds. Pyrroles are one of the most important classes of heterocyclic compounds, because these are readily conducted to important compounds such as porphyrins[9] and polypyrroles.[10] Pyrroles have been conventionally prepared by base-promoted reactions: (i) cyclocondensation of primary amines with 1,4-dicarbonyl compounds (Paal-Knorr synthesis),[11] (ii) cyclocondensation of α-aminoketones or α-oximesters with 1,3-dicarbonyl compounds (Knorr synthesis),[11] and (iii) reactions of isonitriles with nitroolefins (Barton synthesis);[12] however, these methods are composed of more than two reactions and require stoichiometric amounts of strong bases which produce significant amounts of waste salts. Some examples of catalytic synthesis of pyrroles have been reported;[13] however, development of new catalytic methods which proceed highly efficiently and selectively under neutral conditions still remained to be explored.

In the presence of catalyst **1**, cyclocondensation of ethyl isocyanoacetate (**2**) with various 1,3-dicarbonyl compounds proceeds to give the corresponding ethyl pyrrole-2-carboxylates highly selectively (Table 1). When 2,4-pentanedione was used, the condensation product, 3,5-dimethylpyrrole-2-carboxylate (**4**), was obtained exclusively in 84% yield (entry 3). The resultant pyrroles could be readily isolated by short-pass column chromatography or bulb-to-bulb distillation as an analytically pure product. Importantly, a medium-gram scale reaction can be also employed to give **4** in 81% yield. The rhodium-catalyzed reactions gave 2,3,4,5-tetrasubstituted pyrroles in moderate yields (**5a**; 68%, **5b**; 52%) (entry 4), although poor yields have been obtained by conventional methods with strong bases (10−45%).[11c]

The efficiency of the present reaction is demonstrated by regioselective synthesis of pyrroles, which are nearly unaccessible by conventional methods such as Knorr synthesis. The cyclocondensation of **2** with asymmetric 1,3-dicarbonyl compounds ($R^1 \neq R^3$ in eq 2) gives pyrroles regioselectively on the basis of either steric effects or electronic effects. Thus,

(5) (a) Noyori, R.; Ohta, M.; Hisiao, Y.; Kitamura, M.; Ohta, T.; Takaya, H. *J. Am. Chem. Soc.* **1986**, *108*, 7117. (b) Kitamura, M.; Hsiao, Y.; Noyori, R.; Takaya, H. *Tetrahedron Lett.* **1987**, *28*, 4829.

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(11) (a) Jackson, A. H.; Smith, K. H. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiely: New York, 1973; Vol. 1, pp 143−278. (b) Jones, R. A.; Bean, G. P. In *The Chemistry of Pyrroles*; Blomquist, A. T., Wasserman, H. H., Eds.; Academic Press: London, 1977. (c) Patterson, J. M. *Synthesis* **1976**, 281.

(12) (a) Barton, D. H. R.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1985**, 1098. (b) Barton, D. H. R.; Kervagoret, J.; Zard, S. Z. *Tetrahedron* **1990**, *46*, 7587.

(13) (a)Murahashi, S.-I.; Shimamura, T.; Moritani, I. *J. Chem. Soc., Chem. Commun*. **1974**, 931. (b) Utimoto, K.; Miwa, H.; Nozaki, H. *Tetrahedron Lett*. **1981**, *22*, 4277. (c) Chatani, N.; Hanafusa, T. *J. Org. Chem*. **1991**, *56*, 2166. (d) Tsutsui, H.; Narasaka, K. *Chem. Lett*. **1999**, 45.

the reaction of **2** with benzoylacetone gave the corresponding pyrrole **6a** selectively (**6a**/**6b** = 88/12) (entry 5). The structure of the isomer **6a** was determined by NOE experiments and X-ray structure analysis (Figure 1).[14] The reaction

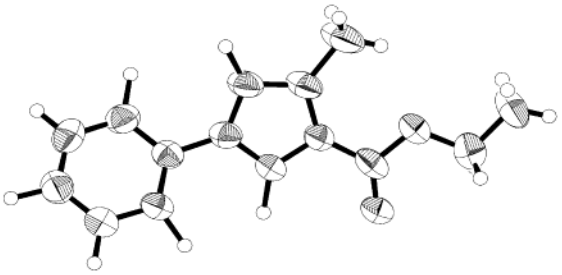


Figure 1. The X-ray structure of **6a**.

of **2** with 1,1,1-trimethyl-2,4-pentanedione gave 5-*tert*-butyl-substituted regioisomer **7** exclusively (entry 6). It is noteworthy that ethyl 2,4-dioxovalerate, which has an electron-withdrawing ester group, gave 3-ethoxycarbonyl-substituted regioisomer **8** exclusively (entry 7). The structure of isomer **8** was unequivocally determined by X-ray structural analysis (Figure 2).[14] The resultant pyrroles thus obtained can be

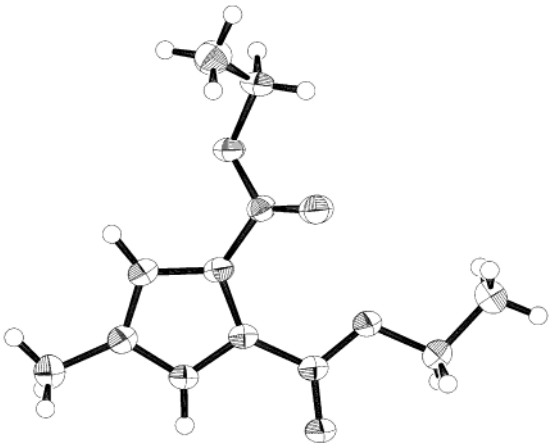


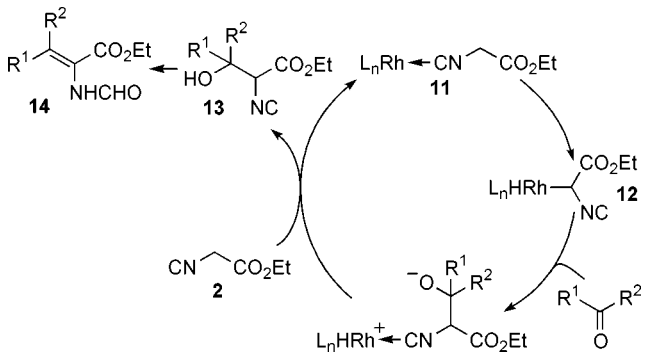
Figure 2. The X-ray structure of **8**.

readily converted to the corresponding porphyrins. Actually, octamethylporphyrin was readily obtained from ethyl 3,4,5-trimethylpyrrole-2-carboxylate (**5a**) by the literature method.[15]

The efficiency of the present reaction is highlighted by the synthesis of fluorinated pyrroles,[16] which are currently the subject of much attention as important building blocks for the synthesis of fluorinated porphyrins[17] and biologically active substances.[18] Thus, the cyclocondensation of **2** with 3-fluoro-2,4-pentanedione gave 3-fluorinated pyrrole **9** (entry 8). Regioselective synthesis of fluorinated pyrroles can be also performed. The reaction of **2** with 2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedione gave 5-*tert*-butyl-substituted pyrrole **10** exclusively (entry 9).

The mechanism for the present reaction can be rationalized by assuming the α-C−H activation of isonitriles shown in Scheme 2. Coordination of isonitrile **2** to the low-valent

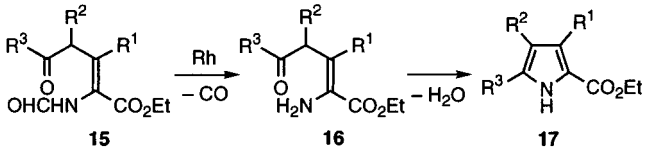
Scheme 2



rhodium complexes RhL_n (L = CO, RNC, PR_3) gives isonitrile complex **11**, and subsequent C−H activation at the α-position of isonitriles could occur to afford isocyanoalkylrhodium intermediate **12**. Insertion of the carbonyl compounds to the rhodium−carbon bond of **12** followed by either reductive elimination or protonation would give **13** and **11** to complete the catalytic cycle. Dehydration and hydration would give the formamide **14** under the reaction conditions.

In the case of the reaction of 1,3-dicarbonyl compounds, intermediate **15** will be formed in place of **14**. Rhodium-promoted decarbonylation[19] of formamide **15** followed by cyclocondensation of enamino intermediate **16** would give the corresponding pyrrole **17** (Scheme 3). The rhodium-

Scheme 3



catalyzed decarbonylation was confirmed by decarbonylation of *N*-phenylformamide. In the presence of 5 mol % of

(14) For details see, the Supporting Infromation.
(15) Paine, J. B., III.; Kirshner, W. B.; Moskowitz, D. W.; Dolphin, D. *J. Org. Chem.* **1976**, *41*, 3857.
(16) For the synthesis of fluorinated pyrroles, see: (a) Kaesler, R. W.; Legoff, E. *J. Org. Chem.* **1982**, *47*, 4779. (b) Ogoshi, H.; Homma, M.; Toi, H.; Aoyama, Y. *Tetrahedron Lett.* **1983**, *24*, 929. (c) Burton, D. J.; Qiu, Z.-M. *Tetrahedron Lett.* **1994**, *35*, 4319. (d) Wang, J.; Scott, A. I. *Tetrahedron* **1994**, *50*, 6181. (e) Leroy, J.; Wakselman, C. *Tetrahedron Lett.* **1994**, *35*, 8605.
(17) (a) Onda, H.; Toi, H.; Aoyama, Y.; Ogoshi, H. *Tetrahedron Lett.* **1985**, *26*, 4221. (b) Tsuchiya, S.; Seno, M. *Chem. Lett.* **1989**, 263. (c) Woller, E. K.; DiMagno, S. G. *J. Org. Chem.* **1997**, *62*, 1588. (d) Leroy, J.; Bondon, A.; Toupet, L.; Rolando, C. *Chem. Eur. J.* **1997**, *3*, 1890. (e) Murahashi, S.-I.; Naota, T.; Komiya, N. *Tetrahedron Lett.* **1995**, *36*, 8059 and references therein.
(18) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123.

catalyst **1**, decarbonylation of *N*-phenylformamide proceeds to give aniline nearly quantitatively under similar reaction conditions. The observed regioselectivity could be ascribed to the selective addition of **12** to the carbonyl group of the 1,3-dicarbonyl compounds. When R^3 is larger than R^1, the addition of the bulky isocyanoalkylrhodium intermediate **12** proceeds at the less hindered carbonyl group adjacent to R^1, giving a pyrrole which has bulky substituent (R^3) at the 5-position. Thus, the reactions of **2** with benzoylacetone and pivaloylacetone proceed selectively to give **6a** and **7**, respectively. On the other hand, when R^1 is larger than R^3 and an electron-withdrawing group, selective addition to the carbonyl group adjacent to R^1 would occur predominantly because of its high electrophilicity, giving a pyrrole which has a bulky and electron-withdrawing substituent (R^1) at the 3-postion. Actually, selective formation of **8** was observed in the reaction of **2** with ethyl 2,4-dioxovalerate. Predominant formation of **10**, which has a bulky *tert*-butyl substituent at 5-position and a strongly electron-withdrawing heptafluoropropane substituent at the 3-position, is compatible with the mechanism.

The present rhodium complex-catalyzed reactions of isonitriles will provide wide scope of both catalytic transformations of isonitriles and new methods for the catalytic synthesis of pyrroles. The key step of the present reaction is the activation of the α-C−H bond of isonitriles induced by the α-heteroatom effect.[1,3]

Acknowledgment. This work was supported by the Research for the Future Program, The Japan Society for the Promotion of Science, and a Grant-in-Aid for Scientific Research, the Ministry of Education, Science, Sports, and Culture, Japan. The authors thank DAIKIN INDUSTRIES, LTD., and Dr. Yoshichika Kuroki for a generous gift of 3-fluoro-2,4-pentanedione.

Supporting Information Available: Experimental procedures, full characterization for all compounds, and crystallographic data for **6a** and **8**. This material is available free charge via the Internet at http://pubs.acs.org.

(19) Zahalka, H. A.; Alper, H. *Tetrahedron Lett.* **1987**, *28*, 2215.

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