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Ruthenium-Catalyzed C−H/CO/Olefin Coupling Reaction of *N*-Arylpyrazoles. Extraordinary Reactivity of *N*-Arylpyrazoles toward Carbonylation at C−H Bonds

Taku Asaumi, Naoto Chatani,* Takuya Matsuo, Fumitoshi Kakiuchi, and Shinji Murai

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

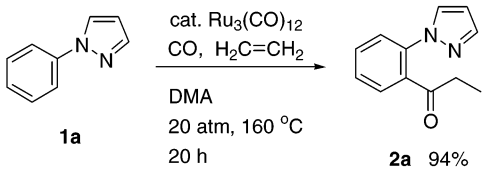
chatani@chem.eng.osaka-u.ac.jp

Received March 10, 2003

Abstract: The reaction of 1-arylpyrazoles with CO and ethylene in the presence of $Ru_3(CO)_{12}$ resulted in regioselective carbonylation at the ortho C−H bonds. While it is found that the pyrazole ring also functions as the directing group for C−H bond cleavage, the efficiency of the reaction depends on the position of the pyrazole ring.

The catalytic formation of a C−C bond from C−H bonds has been extensively studied and it is now recognized as a new synthetic route for the construction of organic molecules.[1] Utilizing the chelation-assistance strategy,[2] a variety of catalytic additions of C−H bonds to alkenes or alkynes have been successfully developed.[3,4] Various types of catalytic carbonylation reactions at C−H bonds have also been reported.[5,6] All substrates which are applicable to direct carbonylation at C−H bonds catalyzed by ruthenium or rhodium involve the sp^2 nitrogen atom as a directing group. This indicates that the coordination of the sp^2 nitrogen to Ru or Rh is an important determinant for the efficiency of the carbonylation reaction. In fact, we have observed a correlation between the pK_a values of conjugate acids of heterocycles (directing group) and the efficiency of carbonylation at C−H bonds α and β to the sp^2 nitrogen.[6f,h] The higher the pK_a is, the more reactive is the molecule. When substrates with a lower pK_a are employed, the reaction must be carried out under lower CO pressure for the reaction to proceed efficiently, because the coordination of the substrates to metal competes with CO. As a result, pK_a values are good indicators of the substrates to be employed. We found that pyrazole also functions as a directing group for carbonylation at C−H bonds in a benzene ring. However, it shows a higher reactivity that would be expected from its pK_a value. In this paper, we wish to report on the $Ru_3(CO)_{12}$-catalyzed reaction of *N*-arylpyrazoles **1** with CO and ethylene.[7]

The reaction of 1-phenyl-1*H*-pyrazole (**1a**, 2 mmol) with CO (20 atm) and ethylene (7 atm) in toluene (6 mL) in the presence of $Ru_3(CO)_{12}$ (0.05 mmol) at 160 °C for 20 h gave 1-[2-(1*H*-pyrazolyl)phenyl]-1-propanone (**2a**)[8] in 62% yield, along with 20% of recovered **1a**. Carbonylation did not take place at a C−H bond on the pyrazole ring, although such a reaction has previously been reported by us.[6h] No second carbonylation products were detected. While investigating the solvent effect, we observed a significant improvement when aprotic polar solvents, such as DMF and DMA (*N*,*N*-dimethylacetamide), were used. The yield increased dramatically to 94% when DMA was used as a solvent (eq 1).[9] The use of common solvents,



(1)

however, had no effect on the yield of **2a** (55% yield (28% **1a** recovered) in THF; 48% (20%) in dioxane; 42% (33%) in CH_3CN).

Some results of reactions with *N*-arylpyrazoles are shown in Table 1. The substitution of an electron-withdrawing group, as in the case of **1d** and **1f**, led to a low conversion, even when the reaction time was extended. The reaction of meta-substituted substrates **1e**

(1) Kakiuchi, F.; Murai, S. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: Berlin, Germany, 1999; pp 47−79. Guari, Y.; Sabo-Etienne, S.; Chaudret, B. *Eur. J. Inorg. Chem*. **1999**, 1047.

(2) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev*. **1993**, *93*, 1307.

(3) For our recent review, see: Kakiuchi, F.; Murai, S. *Acc. Chem. Res*. **2002**, *35*, 826.

(4) For recent papers on C−H/olefin coupling, see: Jun, C.-H.; Moon, C. W.; Hong, J.-B.; Lim, S.-G.; Chung, K.-Y.; Kim, Y.-H. *Chem. Eur. J*. **2002**, *8*, 485. Gupta, S. K.; Weber, W. P. *Macromolecules* **2002**, *35*, 3369. Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc*. **2002**, *124*, 13964.

(5) For our papers on direct carbonylation at C−H bonds in a benzene ring catalyzed by $Ru_3(CO)_{12}$, see: (a) Chatani, N.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Org. Chem*. **1997**, *62*, 2604. (b) Fukuyama, T.; Chatani, N.; Kakiuchi, F.; Murai, S. *J. Org. Chem*. **1997**, *62*, 5647. (c) Ie, Y.; Chatani, N.; Ogo, T.; Marshall, D. R.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem*. **2000**, *65*, 1475.

(6) For papers on chelation-assisted carbonylation at C−H bonds in a heterocyclic ring, see: (a) Moore, E. J.; Pretzer, W. R.; O'Connell, T. J.; Harris, J.; LaBounty, L.; Chou, L.; Grimmer, S. S. *J. Am. Chem. Soc*. **1992**, *114*, 5888. (b) Chatani, N.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc*. **1996**, *118*, 493. (c) Ishii, Y.; Chatani, N.; Kakiuchi, F.; Murai, S. *Organometallics* **1997**, *16*, 3615. (d) Ishii, Y.; Chatani, N.; Kakiuchi, F.; Murai, S. *Tetrahedron Lett*. **1997**, *38*, 7565. (e) Chatani, N.; Ishii, Y.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Org. Chem*. **1998**, *63*, 5129. (f) Fukuyama, T.; Chatani, N.; Tatsumi, J.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc*. **1998**, *120*, 11522. (g) Szewczyk, J. W.; Zuckerman, R. L.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed*. **2001**, *40*, 216. (h) Chatani, N.; Fukuyama, T.; Tatamidani, H.; Kakiuchi, F.; Murai, S. *J. Org. Chem*. **2000**, *65*, 4039. (i) Chatani, N.; Asaumi, T.: Ikeda, T.; Yorimitsu, S.; Ishii, Y.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc*. **2000**, *122*, 12882. (j) Chatani, N.; Yorimitsu, S.; Asaumi, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem*. **2002**, *67*, 7557.

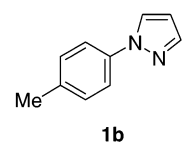
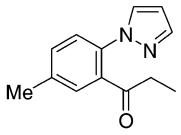
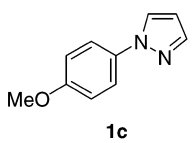
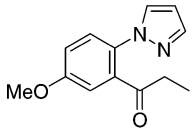
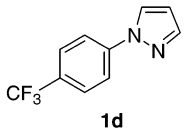
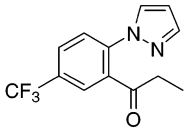
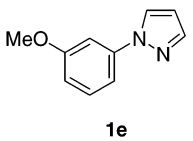
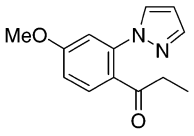
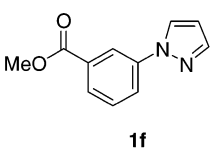
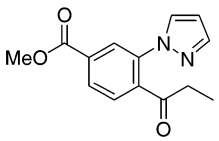
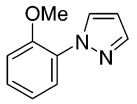
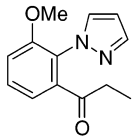
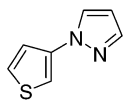
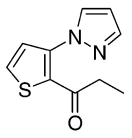
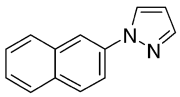
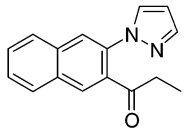
(7) Ellman and Bergman reported on a combinatorial study of the $Ru_3(CO)_{12}$-catalyzed carbonylation reactions at C−H bonds with various types of sp^2 nitrogen containing aromatic heterocycles. It was concluded that *N*-phenylpyrazole is a poor substrate for $Ru_3(CO)_{12}$-catalyzed reactions with CO and *tert*-butylethylene. See ref 6g. We also found that *tert*-butylethylene did not function as an olefin partner, in contrast to ethylene, which has a high reactivity.

(8) All compounds were characterized by NMR, IR, and mass spectral data. For new compounds, elemental analyses or high-resolution mass data were obtained. For full characterization of new compounds, see the Supporting Information.

(9) While the precise role of DMA is not clear, DMA has been shown to be a superior solvent in some $Ru_3(CO)_{12}$-catalyzed carbonylation reactions. Mitsudo, T.; Suzuki, N.; Kobayashi, T.; Kondo, T. *J. Mol. Catal. A* **1999**, *137*, 253. Kondo, T.; Suzuki, N.; Okada, T.; Mitsudo, T. *J. Am. Chem. Soc*. **1997**, *119*, 6187. We also observed a DMA effect on carbonylation at C−H bonds. See ref 6j.

10.1021/jo0343127 CCC: $25.00
Published on Web 08/26/2003

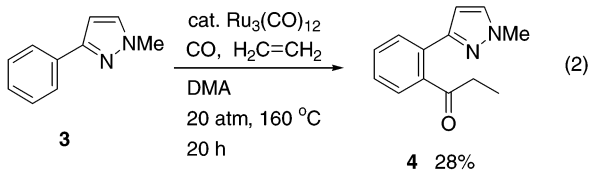
TABLE 1. The $Ru_3(CO)_{12}$-Catalyzed Carbonylation at C−H Bonds in *N*-Arylpyrazoles[a]

pyrazole	product	yield
 **1b**		**2b** 87%
 **1c**		**2c** 87%
 **1d**		**2d** 31% (40% for 60 h)
 **1e**		**2e** 86%
 **1f**		**2f** 45%
 **1g**		**2g** 94%
 **1h**		**2h** 54%
 **1i**		**2i** 86%

[a] Reaction conditions: *N*-arylpyrazole (2 mmol), ethylene (7 atm), CO (20 atm), $Ru_3(CO)_{12}$ (0.05 mmol) in DMA (6 mL) at 160 °C for 20 h. [b] Isolated yields based on *N*-arylpyrazole.

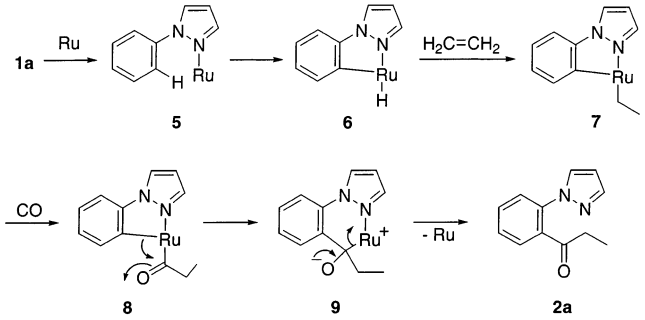
and **1f** resulted in site-selective carbonylation. Thus, carbonylation occurred exclusively at the less hindered C−H bond, irrespective of the electronic nature of the substituents.

The carbonylation of *N*-phenylpyrazoles **1** was found to proceed smoothly. This result is surprising since it was anticipated that *N*-phenylpyrazole might not undergo chelation-assisted direct carbonylation at C−H bonds judging from the pK_a value of the pyrazole ring (2.5).[10] We previously observed a correlation between the efficiency of carbonylation at C−H bonds and the pK_a values of the conjugate acids of heterocycles (directing group). Thus, the higher the pK_a is, the more reactive it will be.[6f,h] In fact, the reactivity decreased in the order 2-phenylpyridine (5.25)[11] > 2-phenylthiazole (2.44)[12] > 2-phenyloxazole (0.8)[13] in the carbonylation at C−H bonds in a benzene ring.[14] It should be noted that the reaction of 1-methyl-3-phenyl-1*H*-pyrazole (**3**) under identical reaction conditions gave the corresponding ketone **4** in 28% isolated yield (eq 2).



(2)

SCHEME 1. A Proposed Mechanism



A proposed mechanism is shown in Scheme 1. The coordination of the sp^2 nitrogen atom in the pyrazole ring in **1a** to Ru directs the metal complex to a desirable C−H bond. The regioselective cleavage of an ortho C−H bond is achieved to give the five-membered ruthenacycle **6**. The hydrometalation of ethylene leads to the formation of an ethyl ruthenium complex **7**, and the insertion of carbon monoxide into the ethyl−Ru bond gives the acyl−Ru intermediate **8**. The reductive elimination from **8** gives **2a**. We propose that the reductive elimination proceeds via the nucleophilic attack of a phenyl group on the carbonyl carbon leading to the formation of a tetrahedral intermediate **9**,[15] from which the cleavage of the C−Ru bond takes place to give the product **2a**, with the regeneration of the active Ru species. This mechanism rationalizes the unexpectedly high reactivity of *N*-arylpyrazoles, in which the electron-donating nature of the nitrogen in the pyrazole ring attached to the benzene ring facilitates the reductive elimination. The significant effect of DMA on product yield can also be rationalized by understanding that the tetrahedral intermediate **9** is

(10) The pK_a value is that of the conjugate acid of 1-methylpyrazole. Reedijk, J. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Ed.; Pergamon Press: Oxford, UK, 1987; Vol. 2, p 73.

(11) The pK_a value is that of the conjugate acid of pyridine. Lide, D. R., Ed. *CRC Handbook of Chemistry and Physics*; CRC Press: Boca Raton, FL, 1990; Section 8.

(12) The pK_a value is that of the conjugate acid of 2-ethylthiazole.

(13) The pK_a value is that of the conjugate acid of 2,4-dimethyloxazole. Brown, D. J.; Ghosh, P. B. *J. Chem. Soc. B* **1969**, 270.

(14) Asaumi, T.; Matsuo T.; Chatani, N. Unpublished data.

(15) A reductive elimination initiated by the inner-sphere attack of one ligand at the π-bond of the other ligand was independently proposed by Hartwig and Buchwald. Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852. Widenhoefer, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 6504.

stabilized by a polar solvent. In addition, the trend in electronic effects of substituents on the benzene ring, in which the electron-donating substituents enhance the reactivity of the substrates, supports this view.

In summary, a pyrazole ring also functions in the direct carbonylation of C−H bonds in a benzene ring. In addition, the unexpectedly higher reactivity of *N*-phenylpyrazoles is due to the facilitation of reductive elimination by the presence of a nitrogen, which is capable of accelerating a nucleophilic attack. Detailed studies of the mechanism of this carbonylation and an examination of new types of substrates for use in carbonylation reactions involving the cleavage of C−H bonds are currently underway.

Acknowledgment. This work was supported, in part, by grants from Monbukagakusho. T.A. acknowledges Research Fellowships of J.S.P.S. for Young Scientists. We thank the Instrumental Analysis Center, Faculty of Engineering, Osaka University, for assistance in obtaining MS, HRMS, and elemental analyses.

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

JO0343127