ORGANIC LETTERS

2008
Vol. 10, No. 2
325−328

Rhodium-Catalyzed One-Pot Synthesis of Substituted Pyridine Derivatives from α,β-Unsaturated Ketoximes and Alkynes

Kanniyappan Parthasarathy, Masilamani Jeganmohan, and Chien-Hong Cheng*

Department of Chemistry, National Tsing Hua University, Hsinchu 30013, Taiwan

chcheng@mx.nthu.edu.tw

Received November 23, 2007

ABSTRACT

A rhodium-catalyzed chelation-assisted C–H activation of α,β-unsaturated ketoximes and the reaction with alkynes to afford highly substituted pyridine derivatives is described.

Recently, considerable research activity has been directed toward the metal-catalyzed C−H bond activation and subsequent carbon−carbon bond formation in organic synthesis.[1] These reactions are environmentally friendly and atom-economical when compared with the other conventional methods such as carbon−halide functionalization.[2,3]

Chelation-assisted activation of the *ortho* aromatic or alkenyl C−H bond by a transition metal complex is a promising and practical method in modern organic synthesis.[1,3] Various directing groups, such as aldehyde, ketone, imine, alcohol, amine, carboxylic acid, and nitrile, have been used to activate the *ortho* aromatic or alkenyl C−H bond. This method has been used for the functionalization of arenes and alkenes[1,3−6] via coupling reactions with organic halides or organometallic reagents[1f,4] and via an addition reaction with carbon−carbon multiple bonds (alkynes or alkenes).[5] However, only very few examples are known for the catalytic activation of alkenyl C−H bond.[6] Moreover, these reactions are mostly limited to β-alkylation of enones, imines, and 2-vinyl pyridines by alkenes.[6] Very recently, Bergman and Ellman reported a rhodium-catalyzed alkylation of α,β-unsaturated aldimines by various alkenes.[7] In the paper, two examples using alkynes as the substrates for the alkenylation of an aldimine were also included. Our continuous interest in metal-catalyzed cyclization reactions[8] prompted us to explore the possibility of α,β-unsaturated ketoximes with alkynes. Herein, we wish to report a new method for the synthesis of highly substituted pyridines from α,β-unsatur-

(1) (a) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (c) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (d) Pastine, S. J.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220. (e) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (f) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174.

(2) (a) Tsuji, J. *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley: New York, 2002. (b) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (c) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635.

(3) Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *J. Am. Chem. Soc.* **2006**, *128*, 11748 and references therein.

(4) Oi, S.; Aizawa, E.; Ogino, Y.; Inoue, Y. *J. Org. Chem.* **2005**, *70*, 3113 references therein.

(5) (a) Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698. (b) Kakiuchi, F.; Matsuura, Y.; Kan, S.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 5936. (c) Masui, K.; Ikegami, H.; Mori, A. J. *Am. Chem. Soc.* **2004**, *126*, 5074 and references therein. (d) Cao, C.; Li, Y.; Shi, Y.; Odom, A. L. *Chem. Commun.* **2004**, 2002. (e) Kuninobu, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2005**, *127*, 13498. (f) Kuninobu, Y.; Tokunaga, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 202.

(6) (a) Kakiuchi, F.; Yamamoto, Y.; Chatani, N.; Murai, S. *Chem. Lett.* **1995**, 681. (b) Jun, C.-H.; Moon, C. W.; Lee, D.-Y. *Chem.—Eur. J.* **2002**, *8*, 2422. (c) Jun, C.-H.; Moon, C. W.; Kim, Y. M.; Lee, J.; Lee, H. *Tetrahedron Lett.* **2002**, *43*, 4233. (d) Lim, S.-G.; Ahn, J.-A.; Jun, C. H. *Org. Lett.* **2004**, *6*, 4687. (e) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 2685. (f) Kakiuchi, F.; Tanaka, Y.; Sato, T.; Chatani, N.; Murai, S. *Chem. Lett.* **1995**, 79. (g) Kakiuchi, F.; Sato, T.; Kakiuchi, F.; Chatani, N.; Murai, S. *Chem. Lett.* **1995**, 893. (h) Chatani, N.; Kamitani, A.; Murai, S. *J. Org. Chem.* **2002**, *67*, 7014.

(7) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 5604.

(8) (a) Rayabarapu, D. K.; Cheng, C.-H. *J. Am. Chem. Soc.* **2002**, *124*, 5630. (b) Bhuvaneswari, S.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2006**, *8*, 5581. (c) Chang, H.-T.; Jayanth, T. T.; Cheng, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 4166.

10.1021/ol7028367 CCC: $40.75
Published on Web 12/20/2007

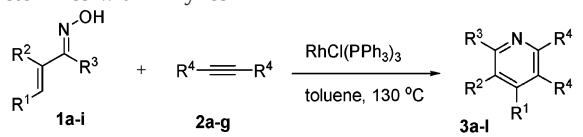
ated ketoximes and alkynes via a rhodium-catalyzed C−H activation of α,β-unsaturated ketoxime. Pyridines are important classes of heterocyclic compounds. The pyridine core is present in various natural products and biologically active compounds.[9] In addition, the starting materials of ketoximes can be prepared readily from the corresponding ketones and hydroxylamine.[10]

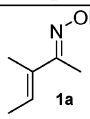
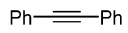
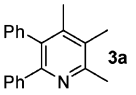
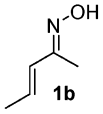
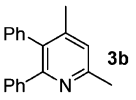
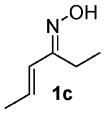
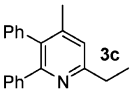
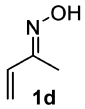
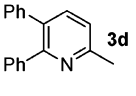
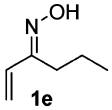
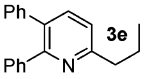
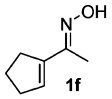
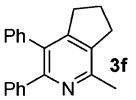
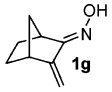
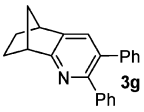
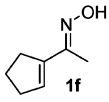
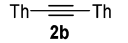
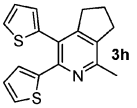
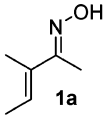
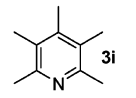
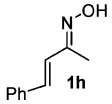
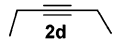
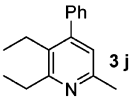
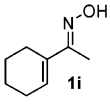
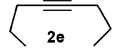
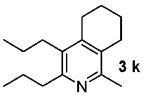
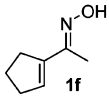
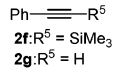
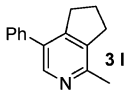
Treatment of α,β-unsaturated ketoxime **1a** having methyl substituents at α- and β-carbons with diphenylacetylene **2a** in the presence of 3 mol % of $RhCl(PPh_3)_3$ in toluene at 130 °C for 3 h gave a highly substituted pyridine derivative **3a** in 92% isolated yield (Table 1, entry 1). To the best of our knowledge, this is the first report using oxime as a directing group for the activation of an alkenyl C−H bond followed by a series of reaction steps leading to the synthesis of N-heteroaromatic compounds.[11] The formation of product **3a** can be viewed as a β-alkenylation of oxime **1a** to provide a 1-azatriene intermediate, followed by a 6π-cyclization and dehydration (vide infra). Alternatively, product **3a** might has been formed via [4 + 2] Diels−Alder cycloaddition of **1a** with **2a**, followed by dehydration.[12] In order to clarify it, the present reaction was carried out in the absence of rhodium catalyst in toluene at 150 °C for 15 h, and no **3a** was obtained. The result indicates that the rhodium catalyst is necessary for the present reaction.

Under similar reaction conditions, several alkyl-substituted α,β-unsaturated ketoximes also react with alkynes **2a** to give the corresponding substituted pyridines. Thus, propenyl methyl ketoxime **1b** and propenyl ethyl ketoxime **1c** gave **3b** and **3c** in 80 and 74% yields, respectively (entries 2 and 3). Similarly, methyl vinyl ketoxime **1d** and propyl vinyl ketoxime **1e** afforded the corresponding pyridine derivatives **3d** and **3e** in moderate 63 and 62% yields, respectively (entries 4 and 5). In addition, α,β-unsaturated cyclic alkenyl oxime, 1-acetylcyclopentene oxime **1f**, reacted with **2a** providing **3f** in 94% yields (entry 6). Interestingly, even oxime **1g** having a [2.2.1] bicyclic moiety reacted efficiently with **2a** to afford the corresponding pyridine derivative **3g** in 68% yield (entry 7).

In addition to diphenylacetylene **2a**, di(2-thienyl)acetylene **2b** also reacts smoothly with unsaturated ketoximes. For example, the reaction of **2b** with **1f** provided highly substituted pyridine derivative **3h** in 89% yield (entry 8). The present catalytic reaction was also successfully extended

Table 1. Results of the Reaction of α,β-Unsaturated Ketoximes with Alkynes[a]



entry	1	2	product 3	yield (%)[b]
1				92
2		2a		80
3		2a		74
4		2a		63[c]
5		2a		62[c]
6		2a		94
7		2a		68[c]
8				89[d]
9				76
10				75
11				81[e]
12				80 51

[a] Unless otherwise mentioned, all reactions were carried out using oximes **1** (1.0 mmol), alkyne **2** (1.1 mmol), $Rh(PPh_3)_3Cl$ (3 mol %), and toluene (2.0 mL) at 130 °C for 3 h. [b] Isolated yields. [c] Reaction time was 12 h. [d] 2-Thienyl. [e] Reaction time was 6 h.

(9) (a) Jones, G. Pyridine and their Benzoderivatives: Synthesis. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 5, pp 167−243. (b) Jayakumar, S.; Ishar, M. P. S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379. (c) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285. (d) Varela, J. A.; Saa, C. *Chem. Rev.* **2004**, *104*, 3787. (e) Movassaghi, M.; Hill, M. D.; Ahmad, O. K. *J. Am. Chem. Soc.* **2007**, *129*, 10096.

(10) (a) Shinada, T.; Yoshihara, K. *Tetrahedron Lett.* **1995**, *36*, 6701. (b) Booth, S. E.; Jenkins, P. R.; Swain, C. J.; Sweeney, J. B. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3499.

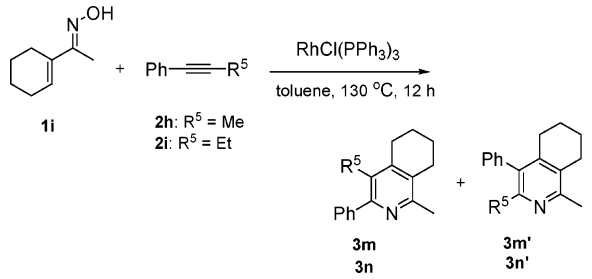
(11) (a) Palladium-catalyzed *O*-methyl oxime as a directing group for activation of the sp^3 C−H bond followed by oxygenation with $PhI(OAc)_2$: Desai, L. V.; Hull, K. L.; Sanford, S. M. *J. Am. Chem. Soc.* **2004**, *126*, 9542. (b) Oxime as a directing group for activation of the *ortho* aromatic C−H bond in a stoichiometric amount of palladium complex: Bezsoudnoba, E. Y.; Ryabov, A. D. *J. Organomet. Chem.* **2001**, *622*, 38.

(12) (a) Boger, D. L.; Ichikawa, S.; Jiang, H. *J. Am. Chem. Soc.* **2000**, *122*, 12169 and references therein. (b) Boger, D. L.; Corbett, W. L.; Curran, T. T.; Kasper. A. M. *J. Am. Chem. Soc.* **1991**, *113*, 1713.

to aliphatic alkynes **2c**−**e**. Thus, **1a** reacted with but-2-yne **2c** to give the corresponding 2,3,4,5,6-pentamethylpyridine **3i** in 76% yield (entry 9). It is interesting to note that oxime **1h** with a phenyl group at the β-carbon reacted smoothly with hex-3-yne **2d** to give the expected pyridine derivative **3j** in 75% yield (entry10) but failed to react with diphenylacetylene **2a**. The steric repulsion between the phenyl groups in **1h** and **2a** likely accounts for the failure of the reaction. Similarly, 1-acetylcyclohexene oxime **1i** reacted nicely with oct-4-yne **2e** to give the pyridine derivative **3k** in 81% yield (entry 11). It is noteworthy that the reaction of α,β-unsaturated aldoxime with alkynes under similar conditions did not give the expected pyridine products. Further studies are required to understand the reaction.[13]

To understand the regioselectivity of the present reaction, unsymmetrical alkynes **2f**−**i** were investigated (Scheme 1).

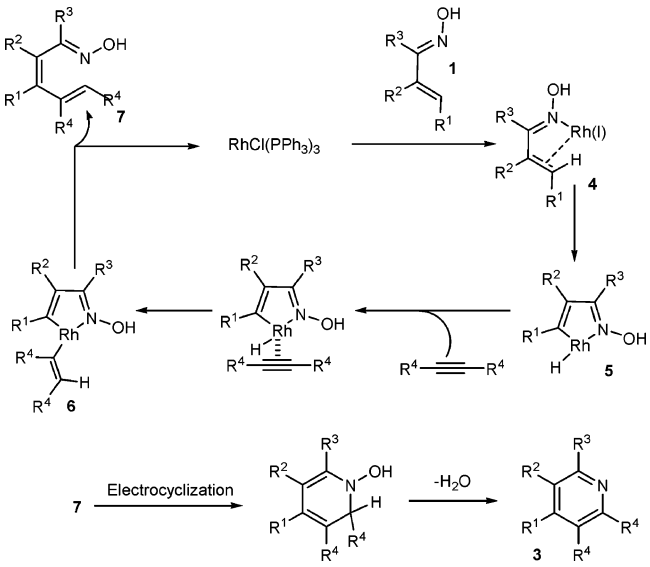
Scheme 1. Rhodium-Catalyzed Reaction of 1-Acetylcyclohexene Oxime **1i** with Unsymmetrical Alkynes **2h**,**i**



1-Phenyl-2-(trimethylsilyl)acetylene (**2f**) efficiently reacted with **1f** in a high regioselective manner, providing desilylated pyridine derivative **3l** in 80% yield in which the Ph group was attached to C-4 of **3l** (Table 1, entry 12). In a similar way, phenylacetylene **2g** gave single regioisomeric product **3l** in 51% yield (Table 1, entry 12). Internal alkyne, 1-phenyl-1-propyne (**2h**), underwent an addition and cyclization reaction with **1i** to give regioisomeric products **3m** and **3m′** in 48 and 30% yields (Scheme 1), respectively. The regiochemistries of **3m** and **3m′** were confirmed by NOE experiments. Similarly, 1-phenyl-1-butyne (**2i**) also afforded two regioisomers **3n** and **3n′** in 75% combined yield with a 78:22 ratio (Scheme 1).

On the basis of known metal-catalyzed directing-group-assisted C−H bond activation reactions,[1,4−7] a possible reaction mechanism is proposed to account for the present catalytic reaction (Scheme 2). The first step involves coordination of the oxime nitrogen of **1** to the rhodium metal followed by oxidative insertion of the alkenyl C−H bond to form a hydrometallacycle **5**.[14] Addition of the rhodium−hydride bond to a coordinated alkyne gives **6**. Subsequent reductive elimination affords C−H addition product **7** and regenerates the catalyst. Product **7** then undergoes 6π-

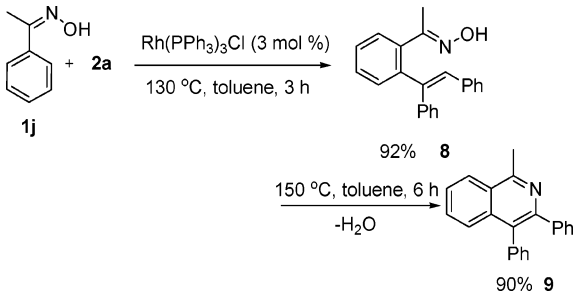
Scheme 2. Proposed Mechanism for the Reaction of α,β-Unsaturated Ketoximes with Alkynes



electrocyclization[15] and elimination of water to give the final pyridine derivative **3**.

To support the proposed mechanism in Scheme 2, we tried to isolate the key product intermediate **7** from α,β-unsaturated ketoximes and alkyne **2a** by lowering the reaction temperature or shortening the reaction time, but the attempt failed. Fortunately, when we extended the catalytic reaction to acetophenone oxime (**1j**) with **2a**, intermediate product **8** was isolated in 92% yield in 3 h. Further, when **8** was refluxed in toluene at 150 °C for 6 h, the corresponding isoquinoline derivative **9** was isolated in 90% yield (Scheme 3). The isolation of **8** and its conversion to product **9** supports strongly the proposed mechanism in Scheme 2.

Scheme 3. Mechanistic Evidence



In conclusion, we have developed a rhodium-catalyzed chelation-assisted C−H activation of α,β-unsaturated ketoxime and the reaction with alkynes to afford substituted pyridine derivatives in good to excellent yields. The method provides an opportunity for the placement of all five sub-

(13) Park, S.; Choi, Y.-A.; Han, H.; Yang, S. H.; Chang, S. *Chem. Commun.* **2003**, 1936.

(14) Jun, C.-H.; Moon, C. W.; Hong, J.-B.; Lim, S. G.; Chung, K.-Y.; Kim, Y.-H. *Chem.*−*Eur. J.* **2002**, *8*, 485.

(15) (a) Trost, B. M.; Gutierrez, A. C. *Org. Lett.* **2007**, *9*, 1473. (b) Tanaka, K.; Mori, H.; Yamamoto, M.; Katsumura, S. *J. Org. Chem.* **2001**, *66*, 3099 and references therein.

stituents (C_2-C_6) of pyridine in one pot. In addition, this appears to be the first report to describe addition of an alkenyl C−H bond to alkynes followed by cyclization and elimination. The present protocol is also successfully applied to the synthesis of an isoquinoline derivative. Further extension of the reaction to other oximes and alkynes, the application of this methodology in natural product synthesis, and the detailed mechanistic investigation are in progress.

Acknowledgment. We thank the National Science Council of the Republic of China (NSC-94-2113-M-007-011) for support of this research.

Supporting Information Available: General experimental procedure and characterization details. This material is available free of charge via the Internet at http://pubs.acs.org.

OL7028367