Synthesis of Pyridine and Isoquinoline Derivatives by the Palladium-Catalyzed Cyclization of Olefinic Ketone *O*-Pentafluorobenzoyloximes

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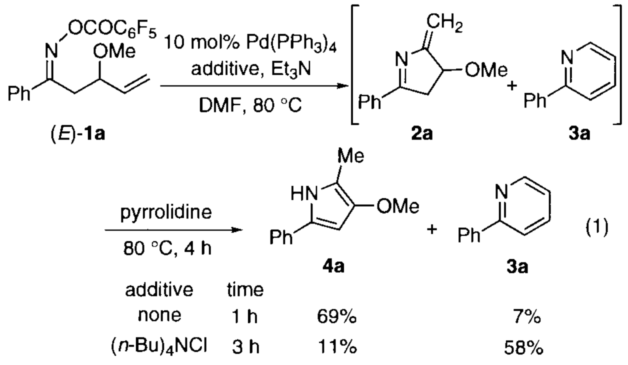
Pyridines and isoquinolines are synthesized from olefinic ketone *O*-pentafluorobenzoyloximes by treatment with a catalytic amount of $Pd(PPh_3)_4$ in the presence of $(n\text{-}Bu)_4NCl$ and triethylamine.

Recently, we have reported the oxidative addition of oxime derivatives to palladium(0) complex to generate alkylideneaminopalladium(II) species.[1,2] This process was applied to the transformation of γ,δ-unsaturated ketone *O*-pentafluorobenzoyloximes to pyrroles by the Heck-type cyclization, and the reaction proceeded regardless of the *E*/*Z* stereochemistry of *O*-pentafluorobenzoyloximes.

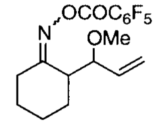
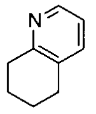
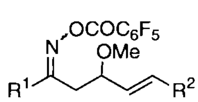
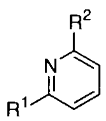
In order to prepare functionalized pyrroles, 3-methoxy-1-phenyl-4-penten-1-one (*E*)-*O*-pentafluorobenzoyloxime (**1a**)[3] was treated with a catalytic amount of $Pd(PPh_3)_4$ in the presence of triethylamine, and the reaction mixture was treated with 10 molar amounts of pyrrolidine.[4] The desired methoxypyrrole **4a** was obtained in 69% yield along with 7% yield of 6-*endo* cyclized product, 2-phenylpyridine (**3a**). By contrast, when this Heck-type reaction was carried out in the presence of 5 molar amounts of $(n\text{-}Bu)_4NCl$,[5] pyridine **3a** was obtained as a main product in 58% yield (eq 1).[6]



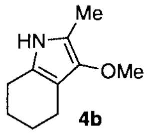
(1)

As shown in Table 1, the palladium-catalyzed cyclization of several β-methoxy γ,δ-unsaturated ketone *O*-pentafluorobenzoyloximes **1** was attempted in the presence of $(n\text{-}Bu)_4NCl$. Although mono 2-alkylated pyridine **3e** was formed in poor yield, disubstituted pyridines **3b–d** were prepared in reasonable yield with a small amount of pyrroles **4**.[7]

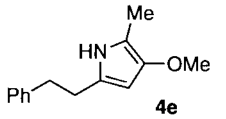
Table 1. Palladium-catalyzed cyclization of β-methoxyketone *O*-pentafluorobenzoyloximes[a]

Oxime	Time / h	Product (Yield / %)
 **1b**[b]	4	 **3b** (62)[c]
		
(*E*)-**1c** (R^1 = Ph, R^2 = Me)	3	**3c** (54)
(*E*)-**1d** (R^1 = Ph, R^2 = Ph)	2.5	**3d** (66)
1e[b] (R^1 = $PhCH_2CH_2$, R^2 = H)	4	**3e** (22)[d]

[a] Oxime : $Pd(PPh_3)_4$: $(n\text{-}Bu)_4NCl$: Et_3N = 1.0 : 0.1 : 5.0 : 5.0. The reaction was conducted in DMF at 80 °C and the reaction mixture was treated with pyrrolidine at 80 °C for 4 h. The concentration of oxime was 0.02 mol dm^{-3}. [b] A mixture of *E* and *Z*-isomers of **1** (*E* : *Z* = 1 : 1) was employed. [c] Methoxypyrrole **4b** was obtained in 21% yield. [d] **4e** was obtained in 19% yield.



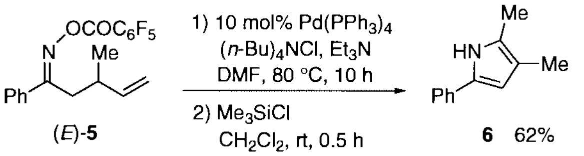
4b



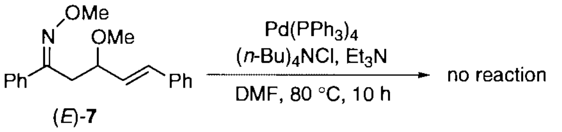
4e

To investigate the course of this formal 6-*endo* cyclization were checked the following reactions. β-Methoxy group is indispensable for the pyridine formation, because the reaction of **5** bearing β-methyl group instead of β-methoxy group gave only trisubstituted pyrrole **6** without forming 4-methyl-2-phenylpyridine (eq 2). *O*-Methyloxime **7** was recovered under the same reaction conditions even by using an equimolar amount of $Pd(PPh_3)_4$ (eq 3). This apparently means that the cyclization does not occur via initial formation of π-allyl palladium species. Murahashi et al. reported the synthesis of pyridines from γ,δ-unsaturated ketone oximes or conjugated dienyl ketone oximes by the palladium(II)-mediated reaction.[6a] Accordingly, the cyclization of conjugated dienyl ketone oxime **8** was examined with a catalytic use of $Pd(PPh_3)_4$ in the presence or absence of $(n\text{-}Bu)_4NCl$, which yielded pyridine **3a** in 61% and 38% yield, respectively (eq 4).[8] On the whole, it is concluded that the oxidative addition of *O*-pentafluorobenzoyloxime **1a** to $Pd(PPh_3)_4$ initially occurs, and the intramolecular coordination of methoxy group to palladium(II) center directs the cyclization to 6-*endo* mode and/or accelerates the elimination of methanol to give dienyl intermediate.

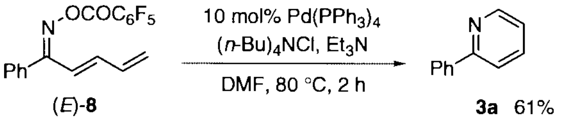
Thus, pyridines are prepared from β-methoxy γ,δ-unsaturated ketone *O*-pentafluorobenzoyloximes by the 6-*endo*-type cyclization. Although pyridines can be also prepared from dienyl oxime derivatives as mentioned above, β-methoxy γ,δ-unsaturated ketones are prepared very easily from silyl enol ethers and α,β-unsaturated aldehyde dimethylacetals.[9]



(2)



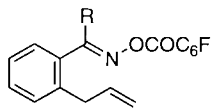
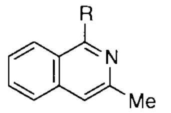
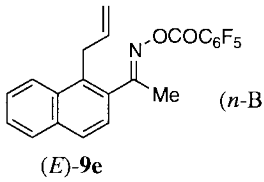
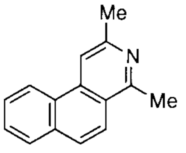
(3)



(4)

Then, we examined the possibility of 6-*exo* cyclization of δ,ε-unsaturated ketone *O*-pentafluorobenzoyloximes by this Heck-type cyclization. Such a cyclization, however, did not proceed smoothly, when acyclic oxime such as ethyl 7-(*O*-pentafluorobenzoyloxy)imino-7-phenyl-2-heptenoate was employed. On the contrary, *O*-pentafluorobenzoyloximes of *o*-allylacetophenone derivatives[10] cyclized to give isoquinoline derivatives. That is, as shown in Table 2, *o*-allylacetophenone *O*-pentafluorobenzoyloxime (**9a**)[11] cyclized to 1,3-dimethylisoquinoline (**10a**) by treatment with the palladium catalyst in the presence of Et_3N–LiCl or Et_3N–$(n\text{-}Bu)_4NCl$ in 61% or 77% yield, respectively (entries 1–3).[12] Some other isoquinoline derivatives **10b–e** were similarly prepared from *o*-allyl-acetophenone derivatives **9** in moderate yield (entries 4–7).

Table 2. Synthesis of isoquinolines by the palladium-catalyzed cyclization of *O*-pentafluorobenzoyloximes[a]

Entry	Oxime	Additive	Time/h	Product(Yield / %)
				
1	(*E*)-**9a** (R = Me)	none	2	**10a** (48)[b]
2	(*E*)-**9a** (R = Me)	LiCl	4	**10a** (61)[c]
3	(*E*)-**9a** (R = Me)	$(n\text{-}Bu)_4NCl$	4	**10a** (77)
4	(*E*)-**9b** (R = Et)	$(n\text{-}Bu)_4NCl$	3	**10b** (63)
5	(*E*)-**9c** (R = Ph)	$(n\text{-}Bu)_4NCl$	10	**10c** (63)
6	(*E*)-**9d** (R = CH_2OMe)	$(n\text{-}Bu)_4NCl$	3	**10d** (55)
7	 (*E*)-**9e**	$(n\text{-}Bu)_4NCl$	3	 **10e** (55)

[a]Oxime : $Pd(PPh_3)_4$: additive : Et_3N = 1.0 : 0.1 : 5.0 : 5.0. The reaction was conducted in DMF at 80 °C. The concentration of oxime was 0.02 mol dm^{-3}. [b]*o*-Allylacetophenone was obtained in 27% yield. [c]*o*-Allylacetophenone was obtained in 7% yield.

References and Notes

1 H. Tsutsui and K. Narasaka, *Chem. Lett.*, **1999**, 45.

2 Recently, Uemura et al. have reported an example of oxidative addition of cyclobutanone oximes to palladium(0) complex. T. Nishimura and S. Uemura, *J. Am. Chem. Soc.*, **122**, 12049 (2000).

3 In the synthesis of 2-methyl-5-phenylpyrrole,[1] *O*-acetyl and *O*-benzoyloximes are not so reactive under the palladium-catalyzed cyclization conditions. For example, it takes 10 h to consume the *O*-benzoyl analogue and the pyrrole is obtained in 35% yield, though the cyclization of *O*-pentafluorobenzoyloxime is complete only 1 h to give the pyrrole in 86% yield.

4 Dihydropyrrole **2a** did not isomerize to pyrrole **4a** by treatment of chlorotrimethylsilane,[1] and **2a** was decomposed.

5 It has been known that the addition of quaternary ammonium halides causes dramatic influence on the reactivity of the Heck reaction, see: B. C. Soderberg, "Transition Metal Alkyl Complexes: Oxidative Addition and Insertion," in "Comprehensive Organometallic Chemistry II," ed. by E. W. Abel, F. G. A. Stone, and G. Wilkinson, Pergamon Press, Oxford (1995), Vol. 12, Chap. 3.5, p. 259; S. Bräse and A. de Meijere, "Palladium-Catalyzed Coupling of Organyl Halides to Alkenes – The Heck Reaction," in "Metal-Catalyzed Cross Coupling Reactions," ed. by P. J. Stang and F. Diederich, John Wiley & Sons, New York (1998), and references cited therein.

6 Palladium-mediated and -catalyzed pyridine, quinoline, and isoquinoline syntheses, see: a) T. Hosokawa, N. Shimo, K. Maeda, A. Sonoda, and S.-I. Murahashi, *Tetrahedron Lett.*, **1976**, 383. b) L. S. Hegedus, G. F. Allen, J. J. Bozell, and E. L. Waterman, *J. Am. Chem. Soc.*, **100**, 5800 (1978). c) A. Kasahara, T. Izumi, and O. Saito, *Chem. Ind.*, **1980**, 666. d) C.-C. Yang, H.-M. Tai, and P.-J. Sun, *J. Chem. Soc., Perkin Trans. 1*, **1997**, 2843.

7 Though the formation of 3,4-dihydro-2*H*-pyrrole **2d** was confirmed by ^1H NMR spectrum of the crude products from **1d**, **2d** did not isomerize to 2-benzyl-3-methoxy-5-phenylpyrrole (**4d**) with pyrrolidine.

8 The dienone oxime **8** did not form from **1a** by treatment with $(n\text{-}Bu)_4NCl$ and triethylamine in DMF at 80 °C.

9 T. Mukaiyama, *Org. React.*, **28**, 203 (1982); T. Mukaiyama, S. Kobayashi, and M. Murakami, *Chem. Lett.*, **1984**, 1759.

10 N. M. Kablaoui, F. A. Hicks, and S. L. Buchwald, *J. Am. Chem. Soc.*, **119**, 4424 (1997).

11 The oxime **9a** was easily prepared by the reaction of *o*-allylacetophenone and hydroxylamine hydrochloride and pyridine, and successively reacted with pentafluorobenzoyl chloride and triethylamine.

12 In the isoquinoline formation from **9**, it was afraid that the reaction proceeded through the isomerization to *o*-vinylacetophenone oximes and the successive 6-*endo* Heck-type cyclization and/or 6π electrocyclization. Such processes, however, can be excluded, because *o*-vinylacetophenone *O*-pentafluorobenzoyloxime did not cyclized to isoquinoline with and without $Pd(PPh_3)_4$.