Direct Synthesis of *β*-Alkenylpyrroles by Pd(II)-Catalyzed Addition of Pyrroles to Alkynoates

Juzo Oyamada, Wenjun Lu, Chengguo Jia, Tsugio Kitamura, and Yuzo Fujiwara*[†]
Department of Applied Chemistry, Faculty of Engineering, Kyushu University, Hakozaki, Fukuoka 812-8581
[†]*Henkel Research Center of Advanced Technology, Molecular Engineering Institute, Kinki University,*
Kayanomori, Iizuka, Fukuoka 820-8555

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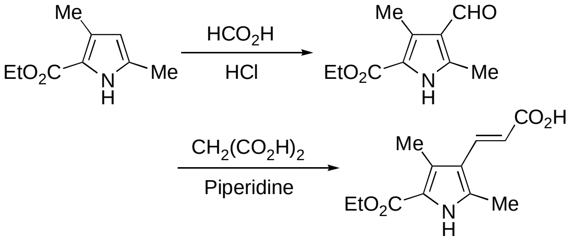
β-Alkenylpyrroles were prepared directly by Pd(II)-catalyzed addition of pyrroles to alkynoates at room temperature. This procedure was applied to direct synthesis of a *β*-alkenylpyrrole, the pyrrole fragment of haemin.

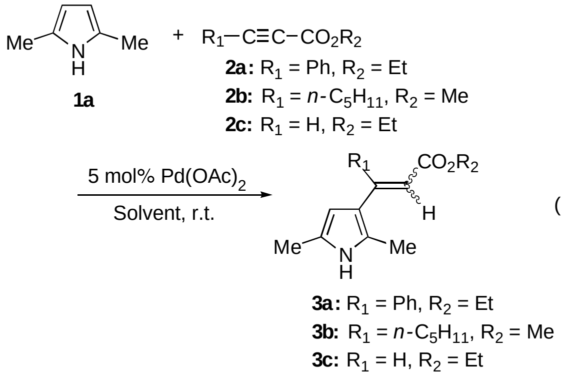
Many pyrroles are subunits of natural products and are the building blocks for porphyrin synthesis.[1] 2,5-Substituted pyrroles are prepared readily since the *α*-positions of pyrroles are favorable for electrophilic aromatic substitution reactions. However, functionalization of *β*-positions of pyrroles are not only interesting for chemists but also significant in the synthesis of natural products.[2] The common method for the preparation of some of these compounds is via conversion from perfunctionalized compounds. For example, for the total synthesis of haemin, a *β*-alkenylpyrrole fragment was prepared from a pyrrole by two steps in Fisher's route as shown in Scheme 1.[3]



Scheme 1.

Recently, we reported that arylolefins could be obtained stereo- and regioselectively by the addition of aromatic compounds to alkynes via C–H activation by Pd(II) or Pt(II) catalysts under very mild conditions.[4] Furthermore, we also found that heteroarenes could add to alkynoates to give the adducts in the presence of a catalytic amount of Pd(OAc)$_2$ in AcOH at room temperature.[5] Then, we extended this method to the most difficult activation of C–H bonds at the *β* positions of pyrroles. Herein, we report the first example of convenient and direct preparation of *β*-alkenylpyrroles by the addition of pyrroles to alkynoates catalyzed by Pd(OAc)$_2$.

As shown in eq (1), the reaction of 2,5-dimethylpyrrole (**1a**) and alkynoates (**2**) in the presence of Pd(OAc)$_2$ at room temperature was examined. When the *α*-positions of pyrrole were occupied as **1a**, the reaction with **2** took place to give the corresponding *β*-alkenylpyrroles (**3**).[6] The results are given in Table 1. In the case of ethyl phenylpropiolate **2a**, *β*-alkenylpyrroles **3a** were obtained as a 2:1 mixture of *E* and *Z* isomers in 71% yield. The reaction with methyl 2-octynoate **2b** gave *β*-alkenylpyrrole **3b** and methyl 3,3-bis(2,5-dimethyl-3-pyrrolyl)octanoate (**4**) in 17 and 35% yields, respectively. However, the same reaction in CH$_2$Cl$_2$ did not occur. When ethyl propiolate **2c** was employed in AcOH in the presence of Pd(OAc)$_2$, **2c** was consumed rapidly in a very short time. Then, the reaction of **1a** and **2c** was conducted in CH$_2$Cl$_2$ and found to give *E*- and *Z*-*β*-alkenylpyrroles **3c** in 29 and 13% yields, respectively.



(1)

Table 1. Pd(II)-Catalyzed alkenylation of **1a** with **2**[a].

Entry	Alkyne	Solvent	Time /h	Product	Yield/%
1	**2a**	AcOH	20	**3a**	71[b]
2	**2b**	AcOH	48[c]	**3b + 4**	52[d]
3	**2b**	CH$_2$Cl$_2$	48[c]	-	-[e]
4	**2c**	CH$_2$Cl$_2$	48[c,f]	**3c**	42[g]

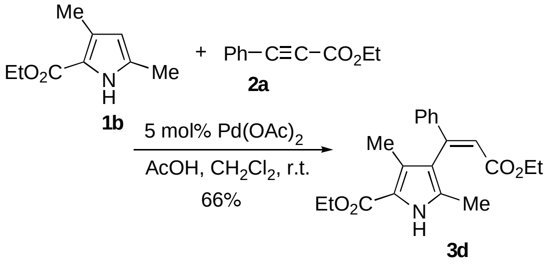
[a]Reaction conditions: **1a** (6 mmol), **2** (3 mmol), Pd(OAc)$_2$ (0.15 mmol), solvent (1 mL), room temperature. [b]A mixture of *E* and *Z*-isomers (E/Z = 2/1). [c]Reaction was conducted under Ar atmosphere. [d]**3b** (17%) and **4** (35%). [e]No reaction. [f]**1a** (8 mmol), **2** (4 mmol) and Pd(OAc)$_2$ (0.2 mmol) were used. [g]*E*-Isomer (29%) and *Z*-isomer (13%).

A typical experimental procedure is as follows: 2,5-dimethylpyrrole **1a** (6 mmol), ethyl phenylpropiolate **2a** (3 mmol), Pd(OAc)$_2$ (0.15 mmol) and AcOH (1 mL) were placed in a 20 mL-tube with a magnetic stirring bar. Then, the mixture was stirred at room temperature for 24 h. After the reaction, the reaction mixture was extracted with ether and washed with water. Then, the organic layer was dried over anhydrous Na$_2$SO$_4$. After the mixture was separated by column chromatography on silica gel with hexane/ethyl acetate (6/1, v/v) as eluent, a mixture of ethyl *E*- and *Z*-3-(2,5-dimethyl-3-pyrroyl)-3-phenyl-2-propenoates **3a** was isolated as yellow crystals in 71% yield.

In our previous studies, it is known that the C–H bond at *α*-positions of pyrroles can be activated by Pd(OAc)$_2$ to react with various alkynoates giving *α*-alkenylpyrroles.[5] Normally, both of reaction rate and yield are good in AcOH. However, CH$_2$Cl$_2$

should be employed as the solvent when the alkynoate reacts with AcOH in the presence of $Pd(OAc)_2$. The stereochemistry of adducts **3** depends on the nature of substituents. The addition of arenes to alkynes proceeds in a *trans* manner.[4] However, the isomerization to the thermodynamically favorable *E* isomer may take place in the present cases.

Further, ethyl 3,5-dimethy-2-pyrrolecarboxylate (**1b**) was used to react with ethyl phenylpropiolate **2a**. The similar reaction of **1b** and **2a** in the presence of $Pd(OAc)_2$ in a mixed solvent of AcOH and CH_2Cl_2 at room temperature for 48 h gave the corresponding β-alkenylpyrrole **3d** in 66% yield [eq (2)]. The *Z* configuration was determined by the NOE experiment.



(2)

In conclusion, we have found a simple and convenient method for the preparation of β-alkenylpyrroles directly from pyrroles and alkynoates in the presence of a catalytic amount of $Pd(OAc)_2$ in AcOH or CH_2Cl_2. The scope and application of this methodology are in progress.

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This paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his 75th birthday.

References and Notes

1 a) R. L. Baxier and A. I. Scott, in "Comprehensive Heterocyclic Chemistry," ed. by A. R. Katritsky and C. W. Rees, Pergamon, Oxford (1984), Vol. 1, p 85. b) G. W. Gibble, in "Comprehensive Heterocyclic Chemistry II," ed. by A. R. Katritsky, C. W. Rees, and E. F. V. Servien, Pergamon, Oxford (1996), Vol. 2, p 207. c) B. Frank and A. Nonn, *Angew. Chem., Int. Ed. Engl.*, **34**, 1795 (1995).

2 a) S. P. J. M. van Nispen, C. Mensink, and A. M. van Leusen, *Tetrahedron Lett.*, **21**, 3723 (1980). b) A. Alvarez, A. Fuzman, A. Ruiz, E. Velarde, and J. M. Muchowski,*J. Org. Chem.*, **57**, 1653 (1992). c) H. Seino, Y. Ishii, and M. Hidai, *J. Am. Chem. Soc.*, **116**, 7433 (1994). d) A. Zelkin, V. R. Shastri, and R. Lange, *J. Org. Chem.*, **64**, 3379 (1999). e) J.-H. Liu, H.-W. Chan, and H. N. C. Wong, *J. Org. Chem.*, **65**, 3274 (2000). f) B. A. Trofimov, L. N. Sobenina, A. I. Mikhalcva, A. P. Demenev, O. A. Tarasova, I. A. Ushakov, and S. V. Zinchenko, *Tetrahedron*, **56**, 7325 (2000).

3 K. C. Nicolaou, D. Vourlournis, N. Winssinger, and P. S. Baran, *Angew. Chem., Int. Ed.*, **39**, 44 (2000).

4 a) C. Jia, D. Piao, J. Oyamada, W. Lu, T. Kitamura, and Y. Fujiwara, *Science*, **287**, 1992 (2000). b) C. Jia, W. Lu, J. Oyamada, T. Kitamura, K. Matsuda, M. Irie, and Y. Fujiwara, *J. Am. Chem. Soc.*, **122**, 7252 (2000).

5 W. Lu, C. Jia, T. Kitamura, and Y. Fujiwara, *Org. Lett.*, **2**, 2927 (2000).

6 **3a** ($E : Z = 2 : 1$): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (t, $J = 7$ Hz, Me), 1.25 (t, $J = 7$ Hz, Me), 1.76 (s, Me), 1.91 (s, Me), 2.13 (s, Me), 2.16 (s, Me), 3.97 (q, $J = 7$ Hz, CH_2), 4.15 (q, $J = 7$ Hz, CH_2), 5.67 (s, =CH), 5.76 (s, =CH), 6.03 (s, pyrrolyl), 6.07 (s, pyrrolyl), 7.21-7.23 (m, Ph), 7.31 (m, Ph), 7.81 (s, NH), 7.93 (s, NH); IR (KBr) 1693 (C=O) cm^{-1}. **3b**: *E*-Isomer, ^{1}H NMR (300 MHz $CDCl_3$) δ 0.88 (t, $J = 7$ Hz, 3H, Me), 1.34 (m, 4H, CH_2), 1.48 (m, 2H, CH_2), 2.22 (s, 3H, Me), 2.34 (s, 3H, Me), 2.95 (t, $J = 7$ Hz, 2H, CH_2), 3.70 (s, 3H, Me), 5.73 (s, 1H, =CH), 5.92 (s, 1H, pyrrolyl), 7.69 (brs, 1H, NH); ^{13}C NMR (75.5 MHz $CDCl_3$) δ 12.75, 13.84, 14.08, 22.56, 29.45, 31.91, 32.18, 50.64, 106.18, 111.67, 121.46, 125.48, 125.68, 158.22, 167.71; IR (KBr) 3334 (N-H), 1687 (C=O) cm^{-1}. **3c**: *E*-Isomer, ^{1}H NMR (300 MHz $CDCl_3$) δ 1.31 (t, $J = 7$ Hz, 3H, Me), 2.20 (s, 3H, Me), 2.28 (s, 3H, Me), 4.21 (q, $J = 7$ Hz, 2H, CH_2), 5.95 (d, $J = 15$ Hz, 1H, =CH), 6.00 (s, 1H, pyrrolyl), 7.62 (d, $J = 15$ Hz, 1H, =CH), 8.01 (brs, 1H, NH); ^{13}C NMR (75.5 MHz $CDCl_3$) δ 11.08, 12.73, 14.40, 59.79, 103.70, 111.05, 117.00, 127.85, 130.75, 138.03, 168.58; IR (KBr) 3328 (N-H), 1689 (C=O) cm^{-1}. *Z*-Isomer, ^{1}H NMR (300 MHz $CDCl_3$) δ 1.30 (t, $J = 7$ Hz, 3H, Me), 2.19 (s, 3H, Me), 2.26 (s, 3H, Me), 4.19 (q, $J = 7$ Hz, 2H, CH_2), 5.49 (d, $J = 13$ Hz, 1H, =CH), 6.74 (d, $J = 13$ Hz, 1H, =CH), 6.88 (s, 1H, pyrrolyl), 7.93 (brs, 1H, NH); ^{13}C NMR (75.5 MHz $CDCl_3$) δ 11.16, 12.67, 14.34, 59.47, 108.12, 109.62, 116.56, 126.33, 132.22, 136.30, 167.25; IR (neat) 3355 (N-H), 1693 (C=O) cm^{-1}. **3d**: ^{1}H NMR (300 MHz $CDCl_3$) δ 1.21 (t, $J = 7$ Hz, 3H, Me), 1.34 (t, $J = 7$ Hz, 3H, Me), 2.01 (s, 3H, Me), 2.02 (s, 3H, Me), 4.11 (q, $J = 7$ Hz, 2H, CH_2), 4.30 (q, $J = 7$ Hz, 2H, CH_2), 6.46 (s, 1H, =CH), 7.34 (m, 5H, Ph), 8.80 (brs, 1H, NH); ^{13}C NMR (75.5 MHz $CDCl_3$) δ 11.37, 12.10, 14.20, 14.53, 59.75, 59.87, 117.71, 118.81, 121.00, 127.62, 127.86, 128.44, 129.29, 131.42, 140.72, 149.86, 161.85, 165.80; IR (KBr) 3274 (N-H), 1720, 1672 (C=O) cm^{-1}. **4**: ^{1}H NMR (300 MHz $CDCl_3$) δ 0.84 (t, $J = 7$ Hz, 3H, Me), 1.23 (m, 6H, CH_2), 1.75 (s, 6H, Me), 2.04 (t, $J = 3.3$ Hz, 2H, CH_2), 2.17 (s, 6H, Me), 2.89 (s, 2H, CH_2), 3.44 (s, 3H, Me), 5.69 (d, $J = 3$ Hz, 2H, pyrrolyl), 7.28 (brs, 2H, NH); ^{13}C NMR (75.5 MHz $CDCl_3$) δ 12.47, 13.04, 14.16, 22.65, 24.06, 32.59, 38.61, 39.94, 43.14, 50.86, 106.30, 121.43, 122.46, 125.02, 172.86; IR (KBr) 3378 (N-H), 1687 (C=O) cm^{-1}.