HETEROCYCLES, Vol. 57, No. 12, 2002, pp. 2261 - 2266, Receivedd, 8th August, 2002

PALLADIUM-CATALYZED SYNTHESIS OF 2,2-DIMETHYL-3-PYRROLINES FROM α-AMINOALLENE AND ARYL IODIDES

Takanori Shibata,* Sho Kadowaki, and Kentaro Takagi

Department of Chemistry, Faculty of Science, Okayama University, Tsushima, Okayama, 700-8530 Japan

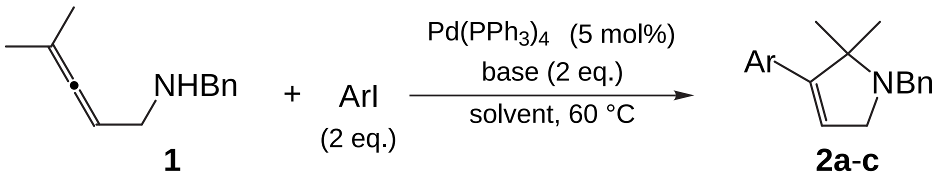
Abstract – Palladium-catalyzed cyclization of dimethyl-substituted allene possessing amino functionality with aryl iodides efficiently proceeded in the presence of diisopropylethylamine to give 2,2-dimethyl-3-aryl-3-pyrrolines. Under an atmospheric pressure of carbon monoxide, 3-aroyl-3-pyrrolines are provided in good yield.

Transition metal-catalyzed reaction using allenes as a three-carbon unit is a useful synthetic method.[1] In particular, palladium complex-catalyzed cyclizations of allenes by intramolecular heteronucleophilic attack is a fascinating route for the preparation of various heterocyclic compounds.[2] For example, the intramolecular reaction of aminoallenes with aryl halides catalyzed by palladium complex proceeds to give many kinds of nitrogen-containing ring systems.[3,4] Syntheses of 3-pyrrolines[5] from α-aminoallenes have been already reported[4b,f,g] but electron-withdrawing groups, like Ts and Mts (2,4,6-trimethylphenylsulfonyl), are used as a protecting group of amino moiety.

We here report that palladium complex-catalyzed cyclization of dimethyl-substituted α-aminoallenes with a benzyl group on nitrogen atom, which is easily deprotected. The choice of base is important for the high yield of products, 2,2-dimethyl-3-aryl-3-pyrrolines.[6] A reaction under an atmospheric pressure of carbon monoxide is also described.

We examined Pd(0) complex-catalyzed reaction of N-benzylallenylamine (**1**)[7] and iodobenzene using inorganic base (Table 1, entry 1). Allenylamine was not completely consumed and 3-pyrroline (**2a**) was obtained as an only detected product but in low yield. After screening of organic bases (entries 2-4), a bulky base was found to be best (entry 4). This is a rare example where diisopropylethylamine efficiently operated as a base in transition metal-catalyzed reactions.[8] 1,2-Dichloroethane (DCE) was also a preferable solvent (entry 5). In 1,2-dimethoxyethane (DME), **1** was readily consumed but to give **2a** in low yield (entry 6). Other aryl groups possessing electron-withdrawing or –donating group could be also introduced to pyrroline ring using 4-methoxyiodobenzene, 4-(ethoxycarbonyl)iodobenzene, respectively and **2b**,**c** were provided in good yield (entries 7,8).

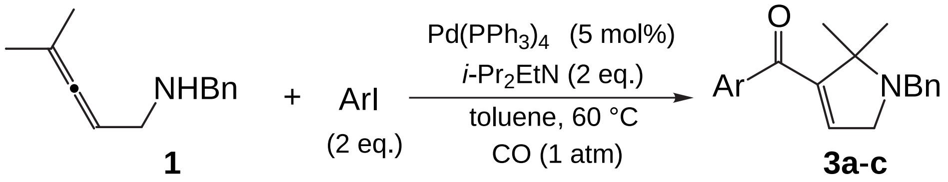
Table 1. Pd-catalyzed cyclization of α-aminoallene (**1**) with aryl iodide



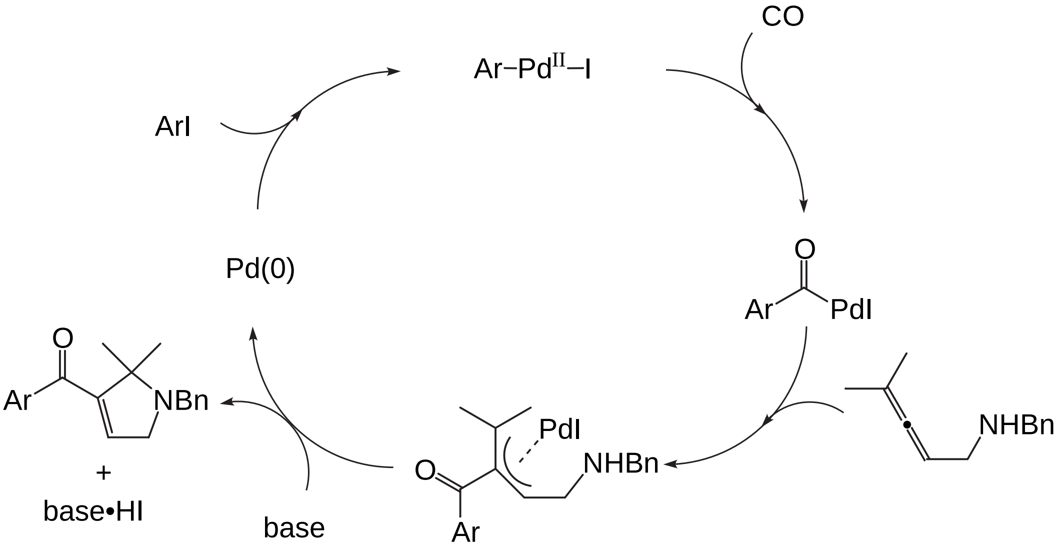
entry	Ar	base	solvent	time/h	yield/%
1	Ph	K_2CO_3	toluene	24	37 (**2a**)
2	Ph	2,6-lutidine	toluene	24	25 (**2a**)
3	Ph	Et_3N	toluene	12	66 (**2a**)
4	Ph	$\underline{\mathrm{i}}\text{-Pr}_2\text{EtN}$	toluene	15	82 (**2a**)
5	Ph	$\underline{\mathrm{i}}\text{-Pr}_2\text{EtN}$	DCE	11	79 (**2a**)
6	Ph	$\underline{\mathrm{i}}\text{-Pr}_2\text{EtN}$	DME	3	33 (**2a**)
7	4-$MeOC_6H_4$	$\underline{\mathrm{i}}\text{-Pr}_2\text{EtN}$	toluene	9	69 (**2b**)
8	4-$EtO_2CC_6H_4$	$\underline{\mathrm{i}}\text{-Pr}_2\text{EtN}$	toluene	7	73 (**2c**)

Next, the same reaction was examined under an atmosphere of carbon monoxide using three aryl iodides (Table 2). Aroyl group was introduced into 3-position of pyrroline ring and the corresponding 3-aroyl-2,2-dimethyl-3-pyrrolines (**3a-c**) were obtained in good yield. It is noteworthy that Pd-catalyzed carbonylative cyclization of aminoallenes smoothly proceeded under an atmospheric pressure of CO.[4g] Carbonylation of arylpalladium complex proceeds to give aroylpalladium complex prior to formation of π-allyl complex from allene.[9] The following cyclization by intramolecular nucleophilic attack of amine moiety to π-allyl complex provide 3- aroyl -3-pyrroline (Scheme 1).

Table 2. Pd-catalyzed carbonylative cyclization of α-aminoallene (**1**) with aryl iodide



entry	Ar	time/h	yield/%
1	Ph	9	73 (**3a**)
2	4-MeOC_6H_4	7	84 (**3b**)
3	4-EtO_2CC_6H_4	7	69 (**3c**)



Scheme 1

In conclusion, we synthesized 2,2-dimethyl-3-pyrrolines by palladium catalyzed cyclization of dimethyl-substituted α-aminoallene using a bulky organic base. At the 3-position of pyrrolines, aryl groups were introduced under an argon atmosphere and aroyl groups under an atmospheric pressure of CO.

EXPERIMENTAL

General. IR spectra were recorded with JASCO FT/IR-5000 spectrophotometer. ^{1}H NMR spectra (200 MHz) were measured with Varian VXR-200 spectrometer using tetramethylsilane (TMS) as an internal standard and $CDCl_3$ was used as solvent. HRMS spectra were obtained with JEOL JMS-SX102A mass spectrometer. Toluene was distilled from calcium hydride and degassed prior to use.

(4-Methylpenta-2,3-dienyl)benzylamine (1). 1 was prepared by the same procedure in the literature[10] from 1-bromo-4-methyl-2,3-pentadiene and benzylamine. Yellow oil; IR (neat) 2910, 1968, 1454, 1114 cm^{-1}; ^{1}H NMR δ= 1.71 (d, 6H, *J*= 2.8 Hz), 3.22 (d, *J*=6.2 Hz, 2H), 3.82 (s, 2H), 5.05-5.08 (m, 1H), 7.24-7.33 (m, 5H); HRMS found m/z 187.1349, calcd for $C_{13}H_{17}N$: 187.1361.

Typical experimental procedure for Pd-catalyzed cyclization (Table 1, entry 4). A mixture of $Pd(PPh_3)_4$ (13.1 mg, 0.011 mmol, 5 mol%), iodobenzene (103.2 mg, 0.453 mmol) and diisopropylethyl-amine (58.5 mg, 0.454 mmol) in toluene (2.5 mL) was stirred under an argon atmosphere for 30 min at 60 °C. A toluene solution (2.0 mL) of allene (**1**) (42.4 mg, 0.226 mmol) was added to the mixture, then the whole was stirred for 15 h at 60℃. The solvent was removed under reduced pressure and the crude products were purified by thin layer chromatography of silica gel (hexane/ethyl acetate=5/1) to give 3-pyrroline (**2a**) (49 .0 mg, 82%).

1-Benzyl-2,2-dimethyl-3-phenyl-3-pyrroline (2a). White solid; mp 36 °C (hexane); IR (neat) 1603, 1493, 1456, 1361 cm^{-1}; ^{1}H NMR δ= 1.33 (s, 6H), 3.38 (d, *J*= 2.2 Hz, 2H), 3.75 (s, 2H), 5.83 (t, *J*= 2.2 Hz, 1H), 7.24-7.43 (m, 10H); HRMS found m/z 263.1676, calcd for $C_{19}H_{21}N$: 263.1674.

1-Benzyl-2,2-dimethyl-3-(4-methoxyphenyl)-3-pyrroline (2b). Yellow solid; mp 82 °C (hexane); IR (neat) 1607, 1512, 1454, 1359, 1253 cm^{-1}; ^{1}H NMR δ= 1.35 (s, 6H), 3.38 (d, *J*= 2.1, 2H), 3.78 (s, 2H), 3.83 (s, 3H), 5.80 (t, *J*= 2.1 Hz, 1H), 6.90 (d, *J*= 8.8 Hz, 2H), 7.26-7.45 (m,7H); HRMS found m/z 293.1773, calcd for $C_{20}H_{23}NO$: 293.1780.

1-Benzyl-2,2-dimethyl-3-(4-ethoxycarbonylphenyl)-3-pyrroline (2c). Yellow solid; mp 92°C (hexane); IR (neat) 1717, 1607, 1456, 1376 cm^{-1}; ^{1}H NMR δ= 1.37 (s, 6H) , 1.41 (t, *J*= 7.2, 3H), 3.42 (d, *J* = 2.2 Hz, 2H), 3.77(s, 2H), 4.39 (q, *J*= 7.2 Hz, 2H), 5.98 (t, *J*= 2.2 Hz, 1H), 7.26-7.48 (m, 7H), 8.02 (d, *J*= 8.4 Hz, 2H); HRMS for (M+1) found m/z 336.1984, calcd for $C_{22}H_{26}NO_2$: 336.1965.

Typical experimental procedure for Pd catalyzed carbonylative cyclization (Table 2). It is the same procedure as above except the reaction was performed under an atmospheric presure of CO.

1-Benzyl-2,2-dimethyl(3-pyrroline-3-yl) phenyl ketone (3a). Yellow oil; IR (neat) 1644, 1325, 1241, 1170 cm^{-1}; ^{1}H NMR δ= 1.46 (s, 6H), 3.48 (d, *J* = 2.2 Hz, 2H), 3.79 (s, 2H), 6.40 (t, *J*= 2.2 Hz, 1H), 7.25-7.53 (m, 8H), 7.76 (d, *J*= 8.8 Hz, 2H); HRMS for (M+1) found m/z 292.1700, calcd for $C_{20}H_{22}NO$:

292.1703.

1-Benzyl-2,2-dimethyl(3-pyrroline-3-yl) 4-metoxyphenyl ketone (3b). Yellow oil; IR (neat) 1642, 1325, 1251, 1166 cm^{-1}; ^{1}H NMR δ= 1.44 (s, 6H), 3.47 (d, *J* =1.7 Hz, 2H), 3.72 (s, 2H), 3.86 (s, 3H), 6.33 (t, *J*= 1.7 Hz, 1H), 6.91 (d, *J*= 8.5 Hz, 2H), 7.26-7.41 (m, 5H), 7.80 (d, *J*= 8.5 Hz, 2H) ; HRMS found m/z 321.1727, calcd for $C_{21}H_{23}NO_2$: 321.1729.

1-Benzyl-2,2-dimethyl(3-pyrroline-3-yl) 4-ethoxycarbonylphenyl ketone (3c). Yellow oil; IR (neat) 1721, 1651, 1278 cm^{-1}; ^{1}H NMR **δ**= 1.40 (t, *J*= 7.1 Hz, 3H), 1.46 (s, 6H), 3.49 (d, *J* =2.0 Hz, 2H), 3.73 (s, 2H), 4.40 (q, *J*= 7.1 Hz, 2H), 6.40 (t, *J*= 2.0 Hz, 1H), 7.26-7.40 (m, 5H), 7.77 (d, *J*= 8.2 Hz, 2H), 8.09 (d, 2H); HRMS for (M+1) found m/z 364.1922, calcd for $C_{23}H_{26}NO_3$:364.1914.

ACKNOWLEDGMENT

This research was supported by a Grant-in-Aid for Scientific Research on Priority Areas (A) "Exploitation of Multi-Element Cyclic Molecules" from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We thank the Center for Instrumental Analysis, Kyushu Institute of Technology for the measurement of analytical data.

REFERENCES

1. Recent reviews, see: (a) Y. Yamamoto and U. Radhakrishnan, *Chem. Soc. Rev.*, 1999, **28**, 199. (b) A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2000, **39**, 3590.
2. Reviews, see: (a) Y. Tamaru and M. Kimura, *Synlett*, 1997, 749. (b) M. Frederickson and R. Grigg, *Org. Prep. Proced. Int.*, 1997, **29**, 63. (c) R. Zimmer, C. U. Dinesh, E. Nadanan, and F. A. Hhan, *Chem. Rev.*, 2000, **100**, 3067.
3. A pioneering work of palladium-catalyzed intermolecular amination of allenes, see: I. Shimizu and J. Tsuji, *Chem. Lett.*, 1984, 233.
4. Recent examples, see: (a) M. Meguro, Y. Yamamoto, and H. Ohno, *Tetrahedron Lett.*, 1998, **39**, 5421. (b) A. Toda, Y. Miwa, T. Taga, E. Osawa, Y. Yamaoka, N. Fujii, and T. Ibuka, *J. Org. Chem.*, 1999, **64**, 2992. (c) F. P. J. T. Rutjes, K. C. M. F. Tjen, L. B. Wolf, W. F. J. Karstens, H. E. Schoemaker, and H, Hiemstra, *Org. Lett.*, 1999, **1**, 717. (d) M. Anzai, A. Toda, H. Ohno, Y. Takemoto, N. Fujii, and T. Ibuka, *Tetrahedron Lett.*, 1999, **40**, 7393. (e) R. Grigg, A. Liu, D. Shaw, S. Suganthan, D. E. Woodall, and G. Yoganathan, *Tetrahedron Lett.*, 2000, **41**, 7125. (f) R. K. Dieter

and H. Yu, *Org. Lett.*, 2001, **3**, 3855. (g) S.-K. Kang and K.-J. Kim, *Org. Lett.*, 2001, **3**, 511. (h) H. Ohno, M. Anzai, A. Toda, S. Ohishi, N. Fujii, T. Tanaka, Y. Takemoto, and T. Ibuka, *J. Org. Chem.*, 2001, **66**, 4904.

5. Other transition metal complex-mediated syntheses of 3-pyrrolines, see: G. Fu and R. H. Grubbs, *J. Am. Chem. Soc.*, 1992, **114**, 7324. (b) H. Kagoshima and T. Akiyama, *J. Am. Chem. Soc.*, 2000, **122**, 11741. (c) M. P. Green, J. C. Prodger, A. E. Sherlock, and C. J. Hayes, *Org. Lett.*, **3**, 3377.
6. A rare example of synthesis of 2,2-dimethyl-3-pyrrolines, see: (a) H.-J. Weintz and P. Binger, *Tetrahedron Lett.*, 1985, **26**, 4075. (b) M. Kimura, H. Harayama, S. Tanaka, and Y. Tamaru, *J. Chem. Soc., Chem. Commun.*, 1994, 2531.
7. As a preliminary experiment, we investigated the effect of substituents on nitrogen using buta-2,3-dienylamine. By the palladium catalyzed reaction with iodobenzene, 2,2-unsubstituted pyrroline derivative was obtained (ca. 20%) from N-benzylbuta-2,3-dienylamine but not from N-tosyl or N-(4-methoxyphenyl)buta-2,3-dienylamine. We decided benzyl as a protecting group for nitrogen of α-aminoallene.
8. (a) S. Murahashi, Y. Imada, Y. Taniguchi, and S. Higashiura, *J. Org. Chem.*, 1993, **58**, 1538. (b) Y. Hashimoto, Y. Horie, M. Hayashi, and K. Saigo, *Tetrahedron: Asymmetry*, 2000, **11**, 2205.
9. (a) R. Grigg, W. S. MacLachlan, D. T. MacPherson, V. Sridharan, S. Suganthan, M. Thornton-Pett, and J. Zhang, *Tetrahedron*, 2000, **56**, 6585. (b) R. Grigg, A. Liu, D. Shaw, S. Suganthan, D. E. Woodall, and G. Yoganathan, *Tetrahedron Lett.*, 2000, **41**, 7125.
10. G. J. Gordon, T. Luker, M. W. Tuckett, R. J. Whitby, and J. Richard, *Tetrahedron*, **2000**, 56, 2113.