Palladium-Catalyzed Synthesis of 1-Azaazulenes from Cycloheptatrienylmethyl Ketone *O*-Pentafluorobenzoyl Oximes

Mitsuru Kitamura, Shunsuke Chiba, Osamu Saku, and Koichi Narasaka*
Department of Chemistry, Graduate School of Science, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033

(Received February 18, 2002; CL-020155)

Substituted 1-azaazulenes are synthesized from cycloheptatrienylmethyl ketone *O*-pentafluorobenzoyloximes by the intramolecular Heck-type amination catalyzed by $Pd(dba)_2$–$(t\text{-}Bu)_3P$.

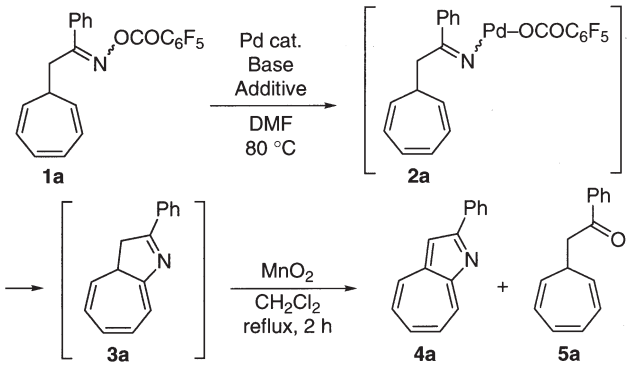
Recently, we reported that N-O bond of oxime derivatives is cleaved by the oxidative addition to Pd(0) complexes to generate alkylidenaminopalladium(II) species.[1] This procedure provides an alternative method to generate alkylidenaminopalladium(II) species which have been prepared previously by the ligand exchange of carbopalladium species with imines.[2] We have demonstrated that Mizoroki-Heck-type cyclization (amino-Heck reaction) of olefinic oxime derivatives proceeds via the aminopalladium complexes, affording various azaarenes such as pyrroles,[1a] pyridines,[1b] isoquinolines,[1b] and spiroimines.[1c]

Although azaazulene derivatives have received much interest for several decades due to their physical properties as azanonbenzenoid aromatics and pharmacological activities,[3] few preparative methods have been known.[3,4] Therefore, we tried to apply this amino-Heck reaction to the synthesis of 1-azaazulenes from cycloheptatrienylmethyl ketone oximes.

By employing 2-(2,4,6-cycloheptatrienyl)-1-phenylethan-1-one *O*-pentafluorobenzoyloxime (**1a**),[5] intramolecular amino-Heck reaction was examined under various reaction conditions as shown in Table 1. After heating a mixture of **1a**, triethylamine, and a catalytic amount of $Pd(PPh_3)_4$ in DMF at 80 °C for 5 h and an usual work up, ^{1}H NMR of the crude mixture exhibited the formation of 3,4-dihydro-2-phenyl-1-azaazulene (**3a**), a small amount of isomers of **3a**, 2-phenyl-1-azaazulene (**4a**), and ketone **5a**. Successive treatment of the crude mixture with MnO_2[4d] gave 1-azaazulene **4a** and ketone **5a** in 25% and 35% yield, respectively (run 1). Addition of MS 4A was effective to increase the yield of 1-azaazulene **4a** and to suppress the ketone formation, as is observed in the previous synthesis of spiroimines[1c] (run 2). When the reaction was carried out by using bis(dibenzylideneacetone)palladium [$Pd(dba)_2$] and $(t\text{-}Bu)_3P$ instead of $Pd(PPh_3)_4$, the yield of **4a** was improved to 78% (run 3). Concerning bases examined, no remarkable influence was observed on the product yields except DBU (runs 4–7).

This method was then applied to the cyclization of various cycloheptatrienyl *O*-pentafluorobenzoyloximes, and the results are summarized in Table 2. In the reaction of **1b** having bulky *tert*-butyl group as R^1 at 80 °C, it required 4.5 h to consume the starting material **1b** and gave the desired 1-azaazulene **4b** in 64% yield, while **4b** was obtained in 84% yield at 110 °C within 0.5 h (run 2). The oximes bearing secondary alkyl groups such as isopropyl and cyclopropyl groups **1c**, **d** cyclized at 80 °C to give the corresponding azaazulenes **4c**, **d** in good yields (runs 3, 4). In contrast, 2-methylazaazulene **4e** was obtained in low yield (run 5). α,β-Unsaturated ketone oxime **1f** having styryl group was converted to 2-styrylazaazulene **4f** in 68% yield (run 6). Alkynyl ketone oxime **1g** gave nitrile **6** via the fragmentation of alkylidenaminopalladium intermediate **2g**[6] (run 7). 2,3-Disubstituted azaazulenes **4h–j** were prepared in moderate yields from α-substituted cycloheptatrienylmethyl ketone oximes **1h–j** (runs 8–10).

Table 1. Synthesis of 1-azaazulene **4a** from oxime **1a**



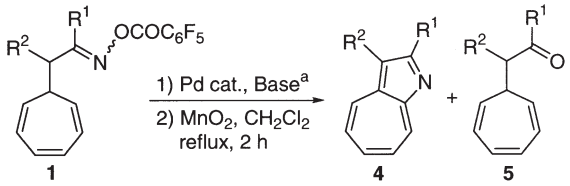
Run	Pd cat. (10 mol%)	Base (3 mol amt)	Additive	Time/h	Yield/%[a] 4a	5a
1	$Pd(PPh_3)_4$	Et_3N	none	5	25	35
2	$Pd(PPh_3)_4$	Et_3N	MS 4A	5	69	21
3	$Pd(dba)_2$ + 4 $(t\text{-}Bu)_3P$	Et_3N	MS 4A	0.5	78	5
4	$Pd(dba)_2$ + 4 $(t\text{-}Bu)_3P$	DBU	MS 4A	1	7	12
5	$Pd(dba)_2$ + 4 $(t\text{-}Bu)_3P$	Cs_2CO_3	MS 4A	1	54	15
6	$Pd(dba)_2$ + 4 $(t\text{-}Bu)_3P$	K_2CO_3	MS 4A	0.8	70	9
7	$Pd(dba)_2$ + 4 $(t\text{-}Bu)_3P$	K_3PO_4	MS 4A	1	74	8

[a]Isolated yield.

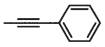
This method can be applied also to the synthesis of polycyclic derivatives. α-Cycloheptatrienyltetralone oxime (**1k**) cyclized to benzo[*g*]cyclohepta[*b*]indole (**8**) and 5,6-Dihydro-benzo[*g*]-cyclohepta[*b*]indole (**9**) in 86% combined yield (eq 1).

Cyclization products of different type were obtained in the reaction of oxime of α-keto ester. 2-(2,4,6-Cycloheptatrienyl)-1-ethoxycarbonylethan-1-one *O*-pentafluorobenzoyloxime (**1l**) underwent the cyclization, leading the desired azulenyl ester **4l** in only 19% yield, and quinoline **10** and isoquinoline **11** were obtained in 33% combined yield[7] (eq 2).

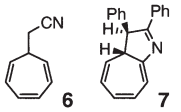
Table 2. Synthesis of azaazulene **4** from oxime **1** by amino-Heck reaction



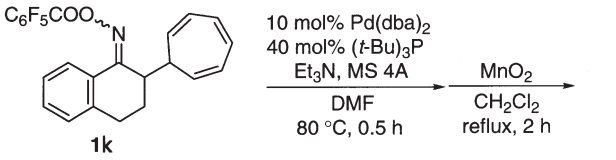
1 4 5

Run	Oxime			Conditions[a]		Yield/%[b]	
	R^1	R^2	**1**	T/°C	Time/h	**4**	**5**
1	Ph	H	**1a**	80	0.5	78	5
2	*t*-Bu	H	**1b**	110	0.5	84	0
3	*i*-Pr	H	**1c**	80	1	62	4
4		H	**1d**	80	1.5	63	5
5	Me	H	**1e**	110	0.3	27	9
6		H	**1f**	80	1	68	2
7[c]		H	**1g**	80	1	0	0
8	Ph	Me	**1h**	110	0.5	52	0
9	Ph	Ph	**1i**	110	0.5	55	4
10[d]	Et	Me	**1j**	110	0.5	42	0

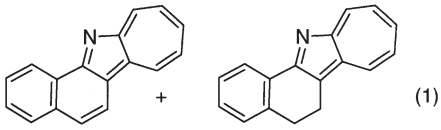
[a]Reaction conditions: 10 mol% $Pd(dba)_2$, 40 mol% (*t*-Bu)$_3$P, 3 mol amt Et_3N, MS 4A, DMF. [b]Isolated yield. [c]See Note 6. [d]**7** was obtained in 21% yield.



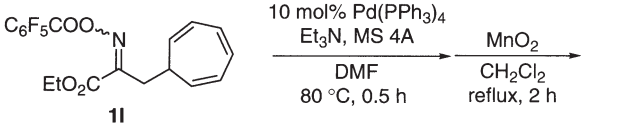
6 **7**



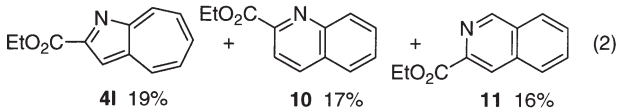
1k



8 50% **9** 36% (1)



1l



4l 19% **10** 17% **11** 16% (2)

As described above, the amino-Heck cyclization of *O*-pentafluorobenzoyloximes of cycloheptatrienylmethyl ketones proceeds by the catalytic use of $Pd(dba)_2$–(*t*-Bu)$_3$P. As the starting materials, oximes **1**, are readily prepared by the addition of ketone derivatives to cycloheptatrienyl tetrafluoroborate[5] and the successive oximation and *O*-pentafluorobenzoylation,[1a] the present method provides a simple procedure to prepare various 2-substituted and 2,3-disubstituted 1-azaazulenes.

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.

References and Notes

1 a) H. Tsutsui and K. Narasaka, *Chem. Lett.*, **1999**, 45. b) H. Tsutsui and K. Narasaka, *Chem. Lett.*, **2001**, 526. c) M. Kitamura, S. Zaman, and K. Narasaka, *Synlett*, **2001**, 974. Recently, palladium(0)-catalyzed synthesis of nitriles from cyclobutanone oximes was reported via alkylidenaminopalladium species; see d) T. Nishimura and S. Uemura, *J. Am. Chem. Soc.*, **122**, 12049 (2000).

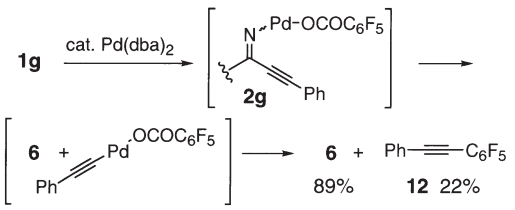
2 J. P. Wolfe, J. Åhman, J. P. Sadighi, R. A. Singer, and S. L. Buchwald, *Tetrahedron Lett.*, **38**, 6367 (1997); G. Mann, J. F. Hartwig, M. S. Driver, and C. Fernández-Rivas, *J. Am. Chem. Soc.*, **120**, 827 (1998).

3 N. Abe, in "Recent Research Developments in Organic and Bioorganic Chemistry," ed. by S. G. Pandalai, Transworld Research Network, Trivandrum (2001), Vol. 4, p 14.

4 a) N. Abe, H. Fujii, K. Tahara, and M. Shiro, *Heterocycles*, **55**, 1659 (2001). b) T. Takayasu and M. Nitta, *J. Chem. Soc., Perkin Trans. 1*, **1999**, 687. c) T. Takayasu, K. Ito, and M. Nitta, *Heterocycles*, **43**, 2667 (1996). d) K. Ito and M. Nitta, *Heterocycles*, **36**, 2247 (1993). e) Y. Sugimura, N. Soma, and Y. Kishida, *Bull. Chem. Soc. Jpn.*, **45**, 3174 (1972).

5 I. D. Reingold, H. A. Trujillo, and B. E. Kahr, *J. Org. Chem.*, **51**, 1627 (1986).

6 Formation of diarylacetylene **12** in the reaction of **1g** (Table 2, run 7) suggested **6** was formed by β-alkynylelimination from **2g** and successive decarboxylation.



7 When the reaction of **1l** was carried out with $Pd(dba)_2$–(*t*-Bu)$_3$P instead of $Pd(PPh_3)_4$, **4l**, **10**, and **11** were obtained in 5, 10, and 10% yields, respectively.