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Palladium-Catalyzed Ring-Opening Reaction of Methyleneaziridines with Carboxylic Acids: Synthesis of α-Amidoketones

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Abstract: In the presence of palladium catalysts, the reaction of methyleneaziridines **1** with carboxylic acids **2** proceeded smoothly to give the corresponding α-amidoketones **3** in good to high yields.

Small ring compounds, such as oxiranes, aziridines, vinylcyclopropanes, and methylenecyclopropanes, have been widely utilized as synthetic intermediates for organic synthesis. Recently a series of methyleneaziridines **1** has been focused on as a new substrate of small heterocycles. Generally, the reaction of methyleneaziridines with strong electrophiles and organometallics proceeds through ring opening at the N−C3 bond (Figure 1, A).[1,2] Although the transition metal-catalyzed reactions of a wide variety of small-ring compounds have been studied for the last several years, the catalytic reactions of methyleneaziridines rarely have been investigated. Alper's group reported palladium-catalyzed carbonylation of methyleneaziridines, which proceeded through N−C2 bond cleavage (B).[3] Quite recently, we found that the hydrocarbonation reaction of the double bond of methyleneaziridines **1** with carbon pronucleophiles proceeded smoothly in the presence of catalytic amounts of palladium giving the non-ring-opened products (C).[4]

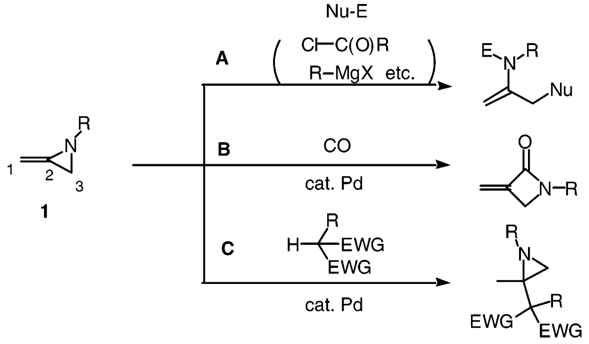
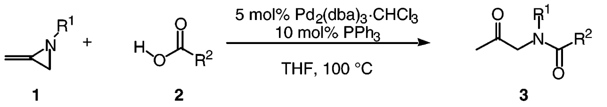


FIGURE 1. The reaction of methyleneaziridines with (A) strong electrophiles and organometallics, (B) carbon monooxide, and (C) active methynes.

We now report that methyleneaziridines **1** react with carboxylic acids **2**, as a pronucleophile, in the presence of a palladium catalyst to give the α-amidoketones **3** in good to high yields (eq 1).



(1)

The results are summarized in Table 1. In the presence of catalytic amounts of $Pd_2(dba)_3$•$CHCl_3$ (5 mol %) and PPh_3 (10 mol %), the reaction of 1-benzyl-2-methyleneaziridine **1a** (0.75 mmol) with acetic acid **2a** (0.5 mmol) in THF at 100 °C gave α-amidoketone **3a** in 75% yield (entry 1). The use of $Pd(PPh_3)_2Cl_2/PPh_3$ as a catalyst was less effective, and $Pd(PPh_3)_2Cl_2$ and $Pd(OAc)_2$ did not promote the reaction at all. The reaction of **1a** and **2a** with other phosphine ligands, such as P(*o*-tolyl)$_3$, P(2-furyl)$_3$, dppf, and P(O)Bu$_3$, instead of PPh_3 afforded **3a** in a lower yield. The reaction in other solvents, such as toluene and acetonitrile, proceeded sluggishly. The reaction of **1a** and **2a** at 60 °C gave **3a** in 51% yield along with a trace amount of the starting material **1a**. In the absence of palladium catalysts, the reaction of **1a** with **2a** in THF at 100 °C gave a complex mixture of unidentified products, indicating that a palladium catalysts is essential to the transformation of **1a** to **3a**. The reactions of **1a** with benzoic acid **2b** and pentenoic acid **2c** afforded **3b** and **3c** in yields of 87% and 71%, respectively (entries 2 and 3). The reaction of **1a** with hippuric acid **2d** proceeded smoothly and the corresponding α-amidoketone **3d** was produced in 57% yield (entry 4). The reaction of 1-hexyl-2-methyleneaziridine **1b** and 1-butyl-2-methyleneaziridine **1c** with **2b** afforded **3e** and **3f** in yields of 69% and 66%, respectively (entries 5 and 6). Methyleneaziridines bearing a methoxy group (**1d**) and or an acetal group (**1e**), upon treatment with **2b**, were converted to **3g** and **3h** in 62% and 67% yield, respectively (entries 7 and 8).

A plausible mechanism for the ring-opening reaction is illustrated in Scheme 1. The oxidative addition of palladium(0) into an O−H bond of the carboxylic acid **2** would give the hydridopalladium complex **4**. The hydropalladation of a double bond of methyleneaziridines **1** with **4** would give **5**. Reductive elimination of palladium(0) would give the N,O-acetal **6**. Thermal rearrangement

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[1] For ring-opening reactions of methyleneaziridines through N−C3 bond cleavage. See: (a) Bottini, A. T.; Roberts, J. D. *J. Am. Chem. Soc.* **1957**, *79*, 1462. (b) Jongejan, E.; Steinberg, H.; De Boer, T. J. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 146. (c) Jongejan, E.; Steinberg, H.; De Boer, T. J. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 66. (d) Ince, J.; Shipman, M.; Ennis, D. S. *Tetrahedron Lett.* **1997**, *38*, 5887. (e) Ennis, D. S.; Ince, J.; Rahman, S.; Shipman, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2047. (f) Quast, H.; Weise Velez, C. A. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 342. (g) Hayes, J. F.; Shipman, M.; Twin, H. *Chem. Commun.* **2000**, 1791. (h) Hayes, J. F.; Shipman, M.; Twin, H. *Chem. Commun.* **2001**, 1784. (i) Hayes, J. F.; Shipman, M.; Twin, H. *J. Org. Chem.* **2002**, *67*, 935. (j) Bottini, A. T.; Roberts, J. D. *J. Am. Chem. Soc.* **1962**, *84*, 195.

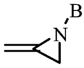
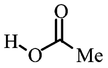
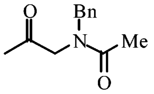
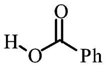
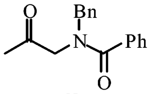
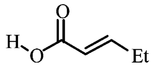
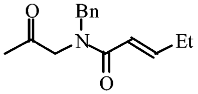
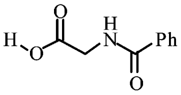
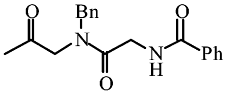
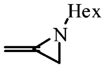
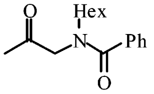
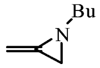
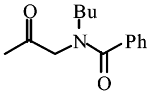
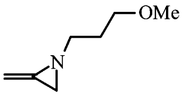
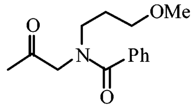
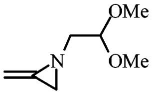
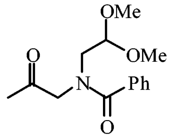
[2] For ring-opening reaction of methyleneaziridines through N−C2 bond cleveage see: Crandall, J. K.; Crawley, L. C.; Komin, J. B. *J. Org. Chem.* **1975**, *40*, 2045.

[3] Pd-catalyzed ring-expansion reaction of methyleneaziridine with carbon monoxide: Pd(0) catalyst inserts into the N−C2 bond of methyleneaziridines: Alper, H.; Hamel, N. *Tetrahedron Lett.* **1987**, *28*, 3237.

[4] Oh, B. H.; Nakamura, I.; Yamamoto, Y. *Tetrahedron Lett.* **2002**, *43*, 9625.

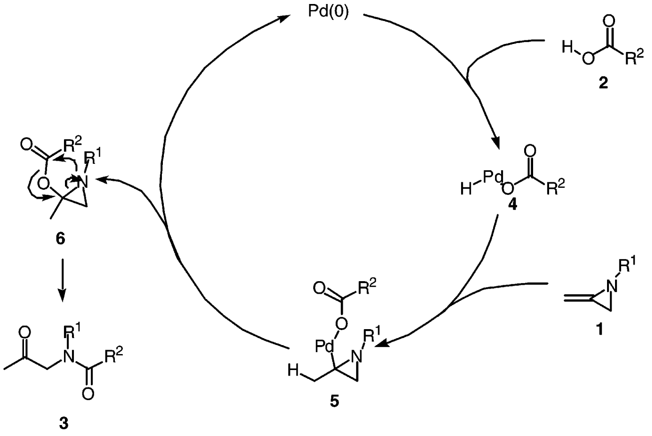
10.1021/jo035739g CCC: $27.50

TABLE 1. Palladium-Catalyzed Ring-Opening Reaction of Methyleneaziridines 1 with Carboxylic Acids 2[a]

entry	1	2	3	yield / %[b]
1	 **1a**	 **2a**	 **3a**	75
2	**1a**	 **2b**	 **3b**	87
3	**1a**	 **2c**	 **3c**	71
4	**1a**	 **2d**	 **3d**	57
5	 **1b**	**2b**	 **3e**	69
6	 **1c**	**2b**	 **3f**	66
7	 **1d**	**2b**	 **3g**	62
8	 **1e**	**2b**	 **3h**	67

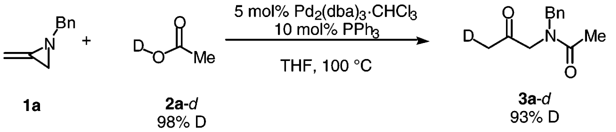
[a] The reaction of **1** (0.75 mmol) and **2** (0.5 mmol) was carried out in the presence of 5 mol % of $Pd_2(dba)_3 \cdot CHCl_3$ and 10 mol % of PPh_3 in THF at 100 °C. [b] Isolated yield based on **2**.

SCHEME 1



of **6** would cleave a N−C2 bond giving α-amidoketone products **3**.[5]

To lend support to the proposed mechanism, the reaction with deuterated acetic acid (**2a**-*d*, 98% D) was carried out. The reaction of **1a** with **2a**-*d* under the same reaction conditions as above gave **3a**-*d* in 70% yield in which the deuterium content at the α-position of **3a**-*d* was 93% (eq 2). This result is in good agreement with the proposed mechanism.



(2)

1a **2a**-*d* 98% D **3a**-*d* 93% D

We and other groups reported the transition metal-catalyzed addition of carboxylic acids to carbon−carbon multiple bonds such as 1,3-dienes,[6] alkynes,[7] enynes,[8] and

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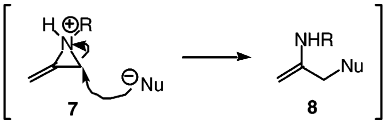
(5) Sato, S.; Kato, H.; Ohta, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2938.

(6) (a) Walker, W. E.; Manyik, R. M.; Atkins, K. E.; Farmer, M. L. *Tetrahedron Lett.* **1970**, *11*, 3817. (b) Rose, D.; Lepper, H. *J. Organomet. Chem.* **1973**, *49*, 473.

(7) (a) Mitsudo, T.; Hori, Y.; Yamakawa, Y.; Watanabe, Y. *J. Org. Chem.* **1987**, *52*, 2230. (b) Doucet, H.; Martin-Vaca, B.; Bruneau, C.; Dixneuf, P. H. *J. Org. Chem.* **1995**, *60*, 7247.

allenes.[9] It is most probable that the ring-opening reaction of methyleneaziridines **1** occurs via the palladium-catalyzed addition of carboxylic acids **2** to the C═C double bond of **1**. Accordingly, it seems that the addition of carboxylic acids to reactive unsaturated C−C multiple bonds is of a class of reactions widely seen in the presence of transition metal catalysts.

It is clear that the palladium-catalyzed ring-opening reaction of methyleneaziridines proceeds through a totally different reaction pathway from the Brønsted acid-promoted ring-opening reaction of methyleneaziridines **1**. The Brønsted acid-promoted reaction proceeds through protonation of a nitrogen atom of methyleneaziridines followed by nucleophilic attack to the aziridine ring (**7**) leading to ring opening at the N−C3 bond (**8**).[1a−c]



In conclusion, we have developed a new method for the synthesis of α-amidoketones via hydrocarboxylation of methyleneaziridines in the presence of a palladium catalyst. The structural unit of α-amidoketones is often found in biologically important compounds such as enzyme inhibitors.[10] It is expected that the present methodology is applicable for such biologically active molecules.[10]

Experimental Section

General Procedure of the Ring-Opening Reaction of Methyleneaziridines 1 with Carboxylic Acids 2. To a mixture of $Pd_2(dba)_3{\cdot}CHCl_3$ (25.9 mg, 0.025 mmol) and triphenylphosphine (13.9 mg, 0.05 mmol) and the carboxylic acid **2** (0.5 mmol) in THF (1 mL) was added methyleneaziridine[12] **1** (0.75 mmol) under Ar atmosphere in a pressure vial. After being heated at 100 °C for 2−5 h, the reaction mixture was filtered through a silica gel column, using ethyl acetate as an eluent. Separation by passage through a silica gel column and purification by middle-pressure liquid column chromatography (silica gel) and recrystallization afforded α-amidoketone **3**.

***N*-Benzyl-*N*-(2-oxopropyl)acetamide (3a).** White solid: IR (KBr) 3035−2937, 1728, 1633, 1494, 1469, 1454, 1419, 1359 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 2.03 (s, 3H, minor), 2.08 (s, 3H, minor), 2.11 (s, 3H, major), 2.22 (s, 3H, major), 4.00 (s, 2H, minor), 4.12 (s, 2H, major), 4.58 (s, 2H, major), 4.60 (s, 2H, minor), 7.17−7.38 (m, 5H, major and m, 5H, minor). ^{13}C NMR ($CDCl_3$, 125 MHz, M = major conformer, m = minor conformer) δ 21.1 (M), 21.3 (m), 27.0 (m), 27.2 (M), 49.5 (m), 52.8 (M), 54.8 (M), 57.1 (m), 126.6 (M), 127.6 (m), 127.8 (M), 128.3 (m), 128.6 (m), 128.9 (M), 136.0 (M), 136.7 (m), 171.0 (m), 171.2 (M), 202.7 (m), 203.1 (M). Anal. Calcd for $C_{12}H_{15}NO_2$ (205.25): C, 70.22; H, 7.37; N, 6.82. Found: C, 70.03; H, 7.50; N, 6.56. HRMS (EI) Calcd for $C_{12}H_{15}NO_2$: *m/z* 205.1103. Found: *m/z* 205.1104.

Supporting Information Available: Experimental information including characterization data of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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