Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 2267–2270

# Synthesis of 1,2,3,4-tetrasubstituted pyrrole derivatives via the palladium-catalyzed reaction of 1,3-diketones with methyleneaziridines

Kalum K. A. D. S. Kathriarachchi, Amal I. Siriwardana, Itaru Nakamura* and Yoshinori Yamamoto

*Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan*

Received 26 December 2006; revised 22 January 2007; accepted 31 January 2007
Available online 4 February 2007

**Abstract**—The palladium-catalyzed reaction of 1,3-diketones **2** with methyleneaziridines **1** produced the corresponding 1,2,3,4-tetrasubstituted pyrroles **3** in good to high yields.


1,2,3,4-Tetrasubstituted pyrroles are often seen in the molecular framework of biologically active compounds, such as lamellarin *O*,[1] lukianol A,[2] and ningalin B,[3] and also have been proven to display antiviral,[4] antibacterial,[5] and antiproliferative activity.[6] Furthermore, these compounds have been utilized as key synthetic intermediates of serotonin antagonists,[7] tumor necrosis factor antagonists,[8] cyclin-dependent kinase inhibitors,[9] and cytosolic phospholipase $A_2$ inhibitors.[10] Due to their characteristic properties, extensive investigations have been made to develop preparative methods for substituted pyrroles. In general, 1,2,3,4-tetrasubstituted pyrroles have been prepared by Knorr reactions,[11] Hantzsch pyrrole synthesis,[12] or 1,3-dipole addition of azomethine ylides with alkynes.[13] These reactions, however, have drawbacks from the synthetic viewpoint, such as the use of stoichiometric amounts of strong bases, lower chemical yields, and formation of undesired byproducts. Recently, transition metal catalyzed reactions, such as intramolecular Heck reaction and hydroamination have been utilized for the synthesis of 1,2,3,4-tetrasubstituted pyrroles.[14] These reactions, however, require highly functionalized starting materials. Accordingly, although several excellent methods have been recently reported,[15] there is still a need to develop a new route for synthesizing these compounds.

Recently, methyleneaziridines of type **1** have been focused on as new synthetic tools in organic synthesis.[16] In general, the reaction of methyleneaziridines with strong electrophiles and organometallics proceeds through ring opening at the N–C3 bond (Fig. 1, **A**).[17] Recently, methyleneaziridine derivatives have been utilized as substrates in transition metal catalyzed reactions. Alper's group reported that palladium-catalyzed carbonylation of methyleneaziridines proceeded through N–C2 bond cleavage (**B**).[18] We found that the hydrocarbonation reaction of the double bond of methyleneaziridines **1** with malononitriles proceeded smoothly in the presence of palladium catalysts, giving the non-ring-opened products (**C**).[19] More recently, we revealed that

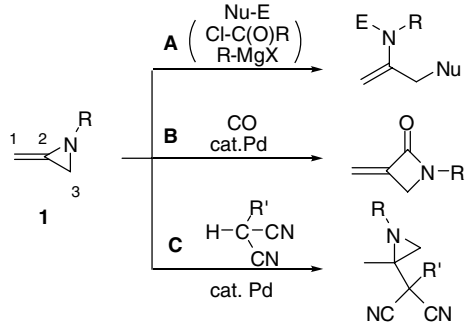
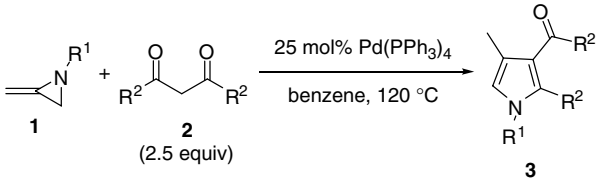



**Figure 1.** The reaction of methyleneaziridines **1** with (**A**) strong electrophiles and organometallics, (**B**) carbon monoxide, and (**C**) malononitriles.

* Corresponding author. Tel.: +81 22 795 6754; fax: +81 22 795 6602; e-mail: itaru-n@mail.tains.tohoku.ac.jp

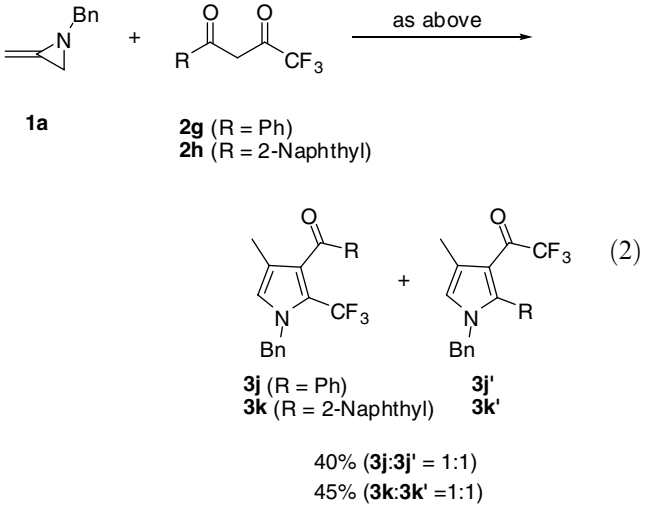
0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.01.170

the palladium-catalyzed reaction of methyleneaziridines with carboxylic acids[20] or methylketones,[21] which had a carbonyl group next to the O–H or C–H bond, proceeded through addition of the O–H or C–H bond to the double bond of **1** followed by ring opening of the aziridine moiety at the N–C2 bond; the reaction of carboxylic acids with **1** afford the corresponding α-amidoketones (Fig. 2, **D**), while that of methylketones gave the corresponding 1,2,4-trisubstituted pyrroles (**E**). Herein, we report that the reaction of methyleneaziridines with 1,3-diketones **2** in the presence of palladium catalysts afforded the corresponding 1,2,3,4-tetrasubstituted pyrroles **3** in good to high yields (Eq. 1).




(1)

The results are summarized in Table 1. The reaction of 1-benzyl-2-methyleneaziridine **1a** (0.3 mmol) and 2,4-pentanedione **2a** (0.75 mmol) in the presence of 25 mol % $Pd(PPh_3)_4$ in benzene proceeded at 120 °C in three days to give 3-acetyl-1-benzyl-2,4-dimethylpyrrole **3a** in 89% yield (entry 1). When 1 equiv of **2a** was used, the yield of **3a** was only 23%. The reaction using other solvents, such as THF, toluene, cyclohexane, and 1,4-dioxane, instead of benzene, gave **3a** in lower yields, while the use of DMF, acetonitrile, or methanol totally interrupted the reaction. The reaction of **1a** with **2a** in the absence of a solvent (neat conditions reported previously)[21] gave **3a** in 30% yield. The reaction **1a** with **2a** in the absence of the palladium catalyst did not proceed at all. Other catalysts, such as $Pd_2(dba)_3{\cdot}CHCl_3$, $Pd(OAc)_2$, $Pt(PPh_3)_4$, $RhCl(PPh_3)_3$, and $Ni(PPh_3)_4$, did not promote the reaction of **1a** with **2a**. The reaction using 10 mol % of $Pd(PPh_3)_4$ afforded **3a** in 72% yield. The reaction of 1-[(4-methylphenyl)methyl]-2-methyleneaziridine **1b** and 1-[(4-ethylphenyl)methyl]-2-methyleneaziridine **1c** with **2a** afforded **3b** and **3c** in yields of 90% and 87%, respectively (entries 2 and 3). The reaction of 1-hexyl-2-methyleneaziridine **1d** with **2a** proceeded smoothly, producing the corresponding pyrrole **3d** in 66% yield (entry 4). The reaction of **1a** and 3,5-heptanedione **2b** gave **3e** in 78% yield (entry 5). The 1,3-cyclohexanediones **2c** and **2d** afforded the corresponding tetrahydroindole derivatives **3f** and **3g** in moderate yields (entries 6 and 7). A 6,7-cyclopentapyrrole derivative **3h** was afforded by the reaction of 1,3-cyclopentanedione **2e** with **1a** (entry 8). The reaction of 1,3-indandione **2f** afforded **3i** in 61% yield (entry 9). Furthermore, the reaction of unsymmetrical 1,3-diketones **2g** or **2h** with **1a** gave a 1:1 mixture of **3j** and **3j′** or **3k** and **3k′** in moderate yields (Eq. 2). Other 1,3-dicarbonyl compounds, such as 3-methyl-2,4-pentanedione, 1,3-diphenylpropane-1,3-dione, ethyl acetoacetate, and diethyl malonate, did not react with **1a** under the reaction conditions.




(2)

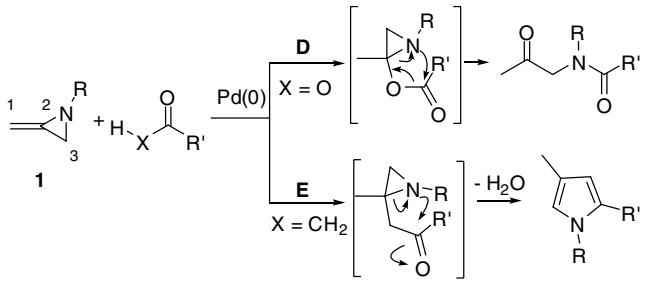
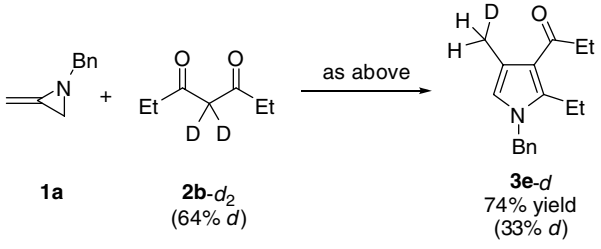



**Figure 2.** Palladium-catalyzed consecutive addition of pronucleophiles-ring opening reaction of methyleneaziridines **1** with (**D**) carboxylic acids (X = O) and (**E**) ketones ($X = CH_2$).

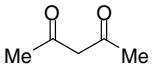
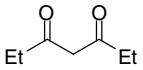
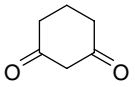
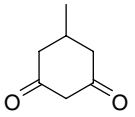
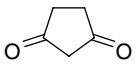
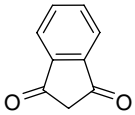
A plausible reaction mechanism is illustrated in Scheme 1. The oxidative insertion of Pd(0) into a carbon–hydrogen bond at the methylene moiety of **2** would lead to the hydridoacetoacetatopalladium species **4**. Hydropalladation of the double bond of **1** with **4** would afford intermediate **5**. Reductive elimination would afford intermediate **6** and Pd(0) species. Thermal ring expansion would lead to zwitterionic intermediate **7** and subsequent elimination of $H_2O$ would give product **3**.

To determine the fate of the hydrogen from the methylene of the 1,3-diketones, we carried out the reaction of 4,4-dideuterio-3,5-heptanedione **2b**-$d_2$, in which the deuterium content of the two hydrogen atoms at the 4-position was 64%, with **1a** under the same reaction conditions (Eq. 3). The deuterated product **3e**-*d*, in which the deuterium content of the methyl group at the 4-position was 33%, was obtained in 74% yield. This result clearly supports the hydropalladation mechanism

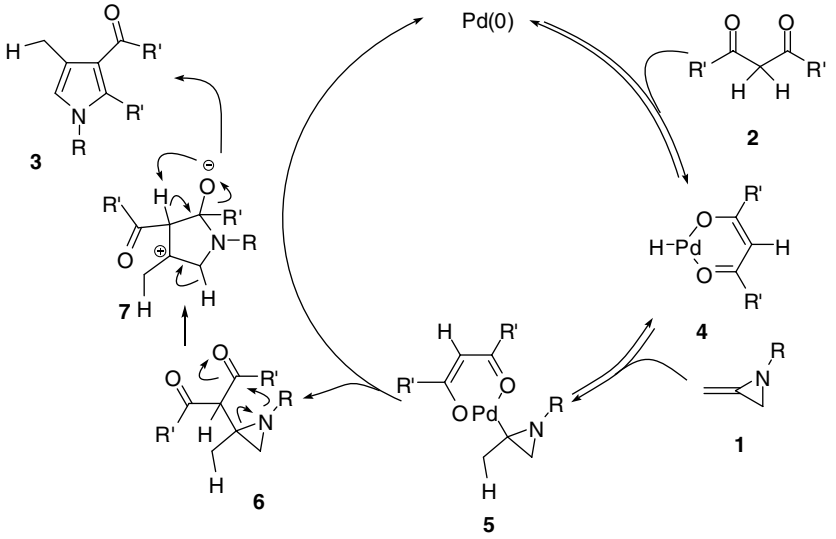



(3)

**Table 1.** Palladium-catalyzed reaction of 1,3-diketones **2** with methyleneaziridines **1**[a]

| Entry | 1 | $R^1$ | 2 | 3 | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | **1a** | Bn |  **2a** | **3a** | 89 |
| 2 | **1b** | *p*-$MeC_6H_4CH_2$ | **2a** | **3b** | 90 |
| 3 | **1c** | *p*-$EtC_6H_4CH_2$ | **2a** | **3c** | 87 |
| 4 | **1d** | *n*-Hex | **2a** | **3d** | 66 |
| 5 | **1a** | Bn |  **2b** | **3e** | 78 |
| 6 | **1a** | Bn |  **2c** | **3f** | 49 |
| 7 | **1a** | Bn |  **2d** | **3g** | 52 |
| 8 | **1a** | Bn |  **2e** | **3h** | 63 |
| 9 | **1a** | Bn |  **2f** | **3i** | 61 |

[a] The reaction of **1** (0.3 mmol) and **2** (0.75 mmol) was carried out in the presence of 25 mol % of $Pd(PPh_3)_4$ in 3 ml of benzene at 120 °C for 3 days.
[b] Isolated yield.




**Scheme 1.** Plausible mechanism.

illustrated in Scheme 1. The observed deuterium content at the methyl group in **3e**-*d* (33%) was higher than the expected value (22%) from deuterium content (64%) in **2b**-$d_2$. This amplification of the deuterium content implies that the hydropalladation of **1** to **5** is reversible.[21]

In conclusion, we have developed a simple and efficient method for the synthesis of various 1,2,3,4-tetrasubstituted pyrrole derivatives using a palladium catalyst without any undesired byproducts. The present reaction represents a new methodology to synthesize these compounds in an efficient and atom economic manner.

*General procedure for the palladium-catalyzed reaction of methyleneaziridines* **1** *with 1,3-diketones* **2**. To 1,3-diketone **2** (0.75 mmol) and $Pd(PPh_3)_4$ (0.075 mmol) in 3 ml of benzene under an argon atmosphere in a pressure vial was added methyleneaziridine **1** (0.3 mmol). The reaction mixture was stirred at 120 °C for 3 days. The reaction mixture was passed through a short silica gel pad and purified by silica gel column chromatography using hexane/ethyl acetate as eluent to obtain **3**.

## Acknowledgement

This work was financially supported by a Grant-in-Aid for Scientific Research from the Japan Society for Promotion in Science (JSPS).

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.170.

## References and notes

1. (a) Urban, S.; Butler, M. S.; Capon, R. J. *Aust. J. Chem.* **1994**, *47*, 1919; (b) Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54.
2. Fürstner, A.; Weintritt, H.; Hupperts, A. *J. Org. Chem.* **1995**, *60*, 6637.
3. (a) Boger, D. L.; Soenen, D. R.; Boyce, C. W.; Hedrick, M. P.; Jin, Q. *J. Org. Chem.* **2000**, *65*, 2479; (b) Bullington, J. L.; Wolff, R. R.; Jackson, P. F. *J. Org. Chem.* **2002**, *67*, 9439.
4. (a) Almerico, A. M.; Diana, P.; Barraja, P.; Dattolo, G.; Mingoia, F.; Loi, A. G.; Scintu, F.; Milia, C.; Puddu, I.; La Colla, P. *Il Farmaco* **1998**, *53*, 33; (b) Almerico, A. M.; Lauria, A.; Diana, P.; Barrajna, P.; Cirrincione, G.; Dattolo, G. *ARKIVOC* **2000**, *(iv)*, 486.
5. Ragno, R.; Marshall, G. R.; Di Santo, R.; Costi, R.; Massa, S.; Rompei, R.; Artico, M. *Bioorg. Med. Chem.* **2000**, *8*, 1423.
6. Padrón, J. M.; Tejedor, D.; Santos-Expósito, A.; García-Tellado, F.; Martín, V. S.; Villar, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2487.
7. North, P. C.; Oxford, A. W. Eur. Pat. Appl. 1988, 35pp, EP 291172 A1 19881117, CAN 110:173233.
8. Kawai, A.; Kawai, M.; Murata, Y.; Takada, J.; Sakakibara, M. PCT Int. Appl. 1998, 95pp, WO 9802430 A1 19980122, CAN 128:140613.
9. (a) Fischer, P. M.; Wang, S.; Wood, G. PCT Int. Appl. 2002, 73pp, WO 2002079193 A1 20021010, CAN 137:294968; (b) Wang, S.; Wood, G.; Meades, C.; Griffiths, G.; Midgley, C.; McNae, I.; McInnes, C.; Anderson, S.; Jackson, W.; Mezna, M.; Yuill, R.; Walkinshaw, M.; Fischer, P. M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4237.
10. (a) Lehr, M. *J. Med. Chem.* **1997**, *40*, 3381; (b) Lehr, M. *Eur. J. Med. Chem.* **1997**, *32*, 805.
11. Knorr, L. *Ber.* **1884**, *17*, 1635.
12. Roomi, M. W.; MacDonald, S. F. *Can. J. Chem.* **1970**, *48*, 1689.
13. (a) Uchida, T. *J. Heterocycl. Chem.* **1978**, *15*, 241; (b) DeShong, P.; Kell, D. A.; Sidler, D. R. *J. Org. Chem.* **1985**, *50*, 2309; (c) Toyota, M.; Nishikawa, Y.; Fukumoto, K. *Heterocycles* **1994**, *39*, 39; (d) Katritzky, A. R.; Yao, J.; Bao, W.; Qi, M.; Steel, P. J. *J. Org. Chem.* **1999**, *64*, 346; (e) Konev, A. S.; Novikov, M. S.; Khlebnikov, A. F. *Tetrahedron Lett.* **2005**, *46*, 8337; (f) Komatsu, M.; Kasano, Y.; Yonemori, J.; Oderaotoshi, Y.; Minakata, S. *Chem. Commun.* **2006**, 526.
14. (a) Dieter, R. K.; Yu, H. *Org. Lett.* **2001**, *3*, 3855; (b) Grigg, R.; Savic, V. *Chem. Commun.* **2000**, 873; (c) Gabriele, B.; Salerno, G.; Fazio, A. *J. Org. Chem.* **2003**, *68*, 7853.
15. Lu, L.; Chen, G.; Ma, S. *Org. Lett.* **2006**, *8*, 835.
16. For a review see: (a) Shipman, M. *Synlett* **2006**, 3205; Preparation of methyleneaziridines; (b) Pollard, C. B.; Parcell, R. F. *J. Am. Chem. Soc.* **1951**, *73*, 2925; (c) De Kimpe, N.; De Smaele, D.; Sakonyi, Z. *J. Org. Chem.* **1997**, *62*, 2448.
17. (a) Cookson, R. C.; Halton, B.; Stevens, I. D. R.; Watts, C. T. *J. Chem. Soc. (C)* **1967**, 928; (b) Bingham, E. M.; Gilbert, J. C. *J. Org. Chem.* **1975**, *40*, 224; (c) Atkinson, R. S.; Malpass, J. R. *Tetrahedron Lett.* **1975**, *16*, 4305; (d) Crandall, J. K.; Komin, J. B. *J. Chem. Soc., Chem. Commun.* **1975**, 436; (e) Crandall, J. K.; Crawley, L. C.; Komin, J. B. *J. Org. Chem.* **1975**, *40*, 2045; (f) Prévost, N.; Shipman, M. *Org. Lett.* **2001**, *3*, 2383; (g) Prié, G.; Prévost, N.; Twin, H.; Fernandes, S. A.; Hayes, J. F.; Shipman, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6517; (h) Margathe, J.-F.; Shipman, M.; Smith, S. C. *Org. Lett.* **2005**, *7*, 4987; (i) Montagne, C.; Shiers, J. J.; Shipman, M. *Tetrahedron Lett.* **2006**, *47*, 9207.
18. Alper, H.; Hamel, N. *Tetrahedron Lett.* **1987**, *28*, 3237.
19. (a) Oh, B. H.; Nakamura, I.; Yamamoto, Y. *Tetrahedron Lett.* **2002**, *43*, 9625; (b) Oh, B. H.; Nakamura, I.; Yamamoto, Y. *ARKIVOC* **2003**, *(viii)*, 67.
20. Oh, B. H.; Nakamura, I.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 2856.
21. Siriwardana, A. I.; Kathriarachchi, K. K. A. D. S.; Nakamura, I.; Gridnev, I. D.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 13898.