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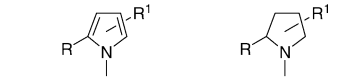
Synthesis of Pyridinylpyrrole Derivatives via the Palladium-Catalyzed Reaction of Acetylpyridines with Methyleneaziridines

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

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

Received July 25, 2004; E-mail: yoshi@yamamoto1.chem.tohoku.ac.jp

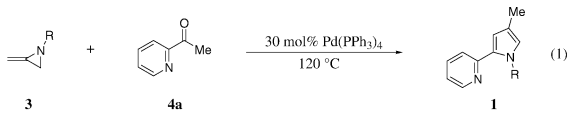
α-Pyridinylpyrroles **1** and their reduced derivatives, pyrrolidines **2**, have attracted considerable interest from pharmaceutical and medicinal chemists due to their biological activities.[1] The synthetic



1 **2**

methodologies for these pyrroles are divided into two major categories: (1) pyridine derivatives, having an alkyl chain with a 1,4-diketone functional group at the ortho, meta, or para position, are synthesized first, and then they are converted to the corresponding pyrroles through the standard procedures;[2] (2) the coupling reaction between α-metallopyrroles and halopyridines (or vice versa) under the Kumada, Negishi, and other conditions gives the desired products **1**.[3] Catalytic hydrogenation of **1** gives pyrrolidine derivatives **2**.[4]

We report herein an entirely new approach for the synthesis of **1** (eq 1). The palladium-catalyzed reaction of the methyleneaziridines **3** with *o*-acetylpyridine **4a** gave the *o*-pyridinylpyrroles **1** in good to high yields. Not only *o*- but also *m*- and *p*-acetylpyridines and related substrates can be used as the starting acetyl derivatives. The results of the reaction of **4a** with **3**, having various R substituents, are summarized in Table 1.



3 **4a** **1**

3a; R = CH_2Ph
3b; R = CH(Me)Ph
3c; R = Hex
3d; R = CH(Me)Cyclohexyl
3e; R = CH_2Ph(*p*-Cl)
3f; R = $CH_2CH(OMe)_2$
3g; R = $CH_2CH_2CH_2OMe$

1a; R = CH_2Ph
1b; R = CH(Me)Ph
1c; R = Hex
1d; R = CH(Me)Cyclohexyl
1e; R = CH_2Ph(*p*-Cl)
1f; R = $CH_2CH(OMe)_2$
1g; R = $CH_2CH_2CH_2OMe$

The reaction of 1-benzyl-2-methyleneaziridine (**3a**, 0.3 mmol) with *o*-acetylpyridine (**4a**, 0.6 mmol) in the presence of 30 mol % of $Pd(PPh_3)_4$ proceeded smoothly at 120 °C without solvent to give the corresponding *o*-pyridinylpyrrole **1a** in 69% yield (entry 1). Other catalysts, such as $Pd_2(dba)_3{\cdot}CHCl_3$, $Pd(OAc)_2$, and $Pt(PPh_3)_4$, did not promote the reaction at all. In the absence of the palladium catalyst, the reaction did not proceed at all, indicating that the palladium catalyst is essential to make the above transformation feasible. In the presence of additional phosphine ligands, such as dppe, dppb, $P(OBu)_3$, and extra PPh_3, unsatisfactory results were obtained. Normally, 2 equiv of *o*-acetylpyridine was used. When 1 equiv of **4a** was used, the yield of **1a** decreased to 55%. Likewise, the reactions of **3b**, **3c**, and **3d** proceeded smoothly to afford **1b**, **1c**, and **1d**, respectively, in good to high yields (entries 2−4). The reaction of **3e** bearing an electron-withdrawing functional group gave **1e** in a moderate yield (entry 5). Furthermore, the reactions of **3f** and **3g** proceeded smoothly, producing **1f** and **1g** in 78% and 74% yields, respectively (entries 6 and 7).

Table 1. Palladium-Catalyzed Reactions of *o*-Acetylpyridine **4a** with the Methyleneaziridines **3**[a]

entry	3	product 1	yield of 1/%[b]
1	**3a**	**1a**	69
2	**3b**	**1b**	75
3	**3c**	**1c**	74
4	**3d**	**1d**	87
5	**3e**	**1e**	43
6	**3f**	**1f**	78
7	**3g**	**1g**	74

[a] The reaction of **3** (0.3 mmol) with **4a** (0.6 mmol) was carried out in the presence of 30 mol % $Pd(PPh_3)_4$ without solvent at 120 °C for 3 days in a pressure vial under Ar atmosphere. [b] Isolated yield based on **3**.

Scheme 1

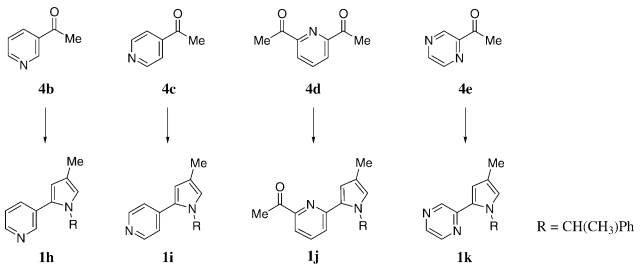


Table 2. Palladium-Catalyzed Reactions of Various Acetylpyridines **4b**−**d** and Acetylpyrazine **4e** with **3b**[a]

entry	4	product 1	yield of 1/%[b]
1	**4b**	**1h**	72
2	**4c**	**1i**	88
3	**4d**	**1j**	72
4	**4e**	**1k**	96

[a] The reaction of **3b** (0.3 mmol) with **4** (0.6 mmol) was carried out in the presence of 30 mol % $Pd(PPh_3)_4$ without solvent at 120 °C for 3 days. [b] Isolated yield based on **3b**.

We extended the new methodology to synthesize the *m*- and *p*-pyridinylpyrroles and related compounds **1h**−**k** (Scheme 1, Table 2). The reaction of **3b** with the *m*- and *p*-pyridine derivatives, **4b** and **4c**, afforded **1h** and **1i** in 72% and 88% yield, respectively (entries 1 and 2). Similarly, **4d** and **4e** gave the corresponding pyrroles **1j** and **1k**, respectively, in good to high yields (entries 3 and 4).

A plausible mechanism is shown in Scheme 2. The oxidative insertion of Pd(0) into an α-carbon−hydrogen bond of *o*-acetylpyridine **4a** produces the hydridopalladium species **5**[5] (or its oxa-π-allyl structure **5′**), and then the hydropalladation of **3** with **5** takes place as shown in **6**. Reductive elimination of palladium may then

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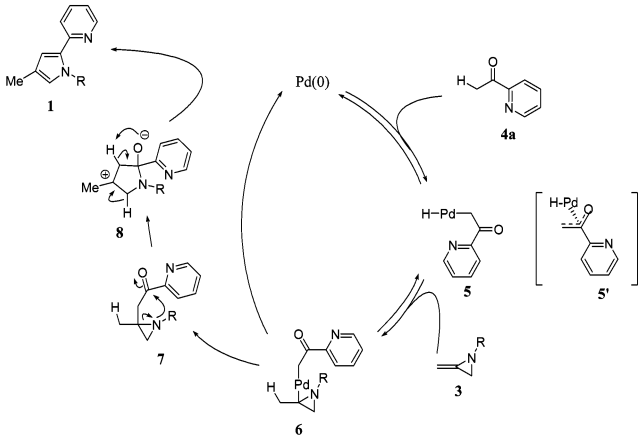
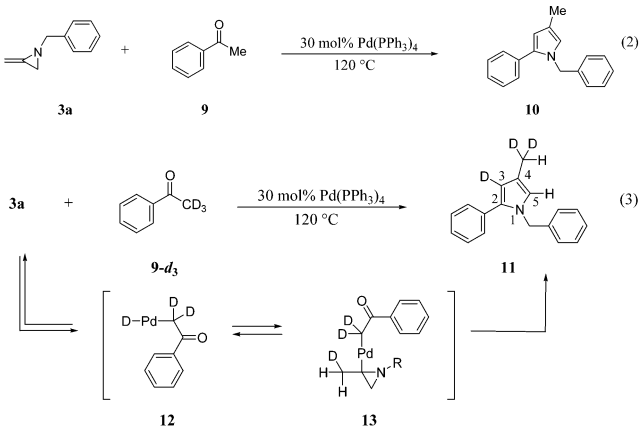
Scheme 2. Plausible Mechanism for the Formation of *o*-Pyridinylpyrrole **1**



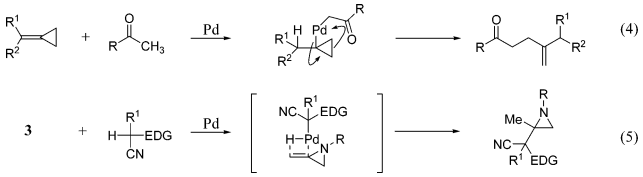
occur to afford the intermediate **7** and Pd(0) species. Subsequent cyclization affords the intermediate **8**, and elimination of H_2O produces **1** (see also the Supporting Information and ref 6).

The fact that not only the *o*- but also the *m*- and *p*-acetylpyridines undergo rather facile pyrrole formation strongly suggests that a chelation effect of the nitrogen of pyridine ring on the Pd(0) insertion step is not essential but the acidity of α-C−H group is a key for the present interesting transformation.

The reaction of **3a** with acetophenone **9** under the same conditions as above gave **10** in 95% yield (eq 2), indicating that the chelation effect of nitrogen of pyridine is not operative. The structure of **10** was confirmed unambiguously by synthesizing its authentic sample through the reported procedure.[7] To confirm the proposed mechanism, the reaction of deuterated acetophenone **9**-d_3 with **3a** was carried out under the same reaction conditions as shown in eq 2, giving the deuterated product **11** (*d* content at C-3 and CH_3 was about 70%) in 82% isolated yield, together with recovered **9**-d_3 (*d* content at CH_3 group was 55%, eq 3, see also Supporting Information). Two deuteriums were labeled at CH_3 of **11**, probably because the equilibration occurs via reversible β-H (or β-D) elimination of **13**. A strong support for the hydropalladation mechanism was obtained by the fact that the deuterium labeling occurred at C-3 of **11**.



The palladium-catalyzed reaction of methyl ketones with methylenecyclopropanes (MCPs) gives the α-allylated ketones in good yields, in which the α-C−H insertion of Pd(0) followed by hydropalladation of the C═C double bond of MCP is proposed as a plausible mechanism (eq 4).[8] The reaction of activated methynes with **3** affords the hydrocarbonation products, in which hydropalladation to the C═C double bond of **3** is proposed (eq 5).[9] The presence of a ketone group in the pertinent position of **6** would make it possible to lead to the ring-closing reaction (**7** → **8**).



We have developed a simple and efficient method for the synthesis of various pyridinylpyrroles using palladium catalyst. Moderate to good yields of the products are obtained in all cases, and a wide range of acetyl aromatics and hetarenes can be used as a starting material, which makes it feasible to synthesize biologically very important pyridinylpyrrole derivatives and related compounds.

Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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