Synthesis of Imidazoles and Pyrimidines Using Palladium-Catalyzed Decarboxylative Intramolecular Condensation of 1,2,4-Oxadiazol-5(4*H*)-ones

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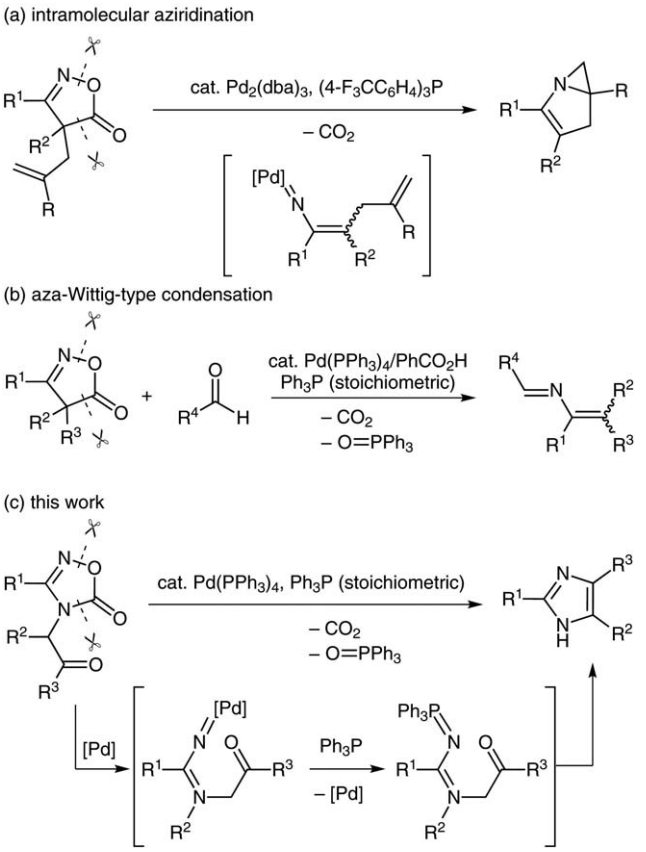
Abstract: We found that 1,2,4-oxadiazol-5(4*H*)-ones acted as iminonitrene equivalents in the presence of a palladium catalyst and a stoichiometric amount of phosphine and that aza-Wittig-type condensation with the internal carbonyl moiety occurred to afford the corresponding imidazoles and pyrimidines.

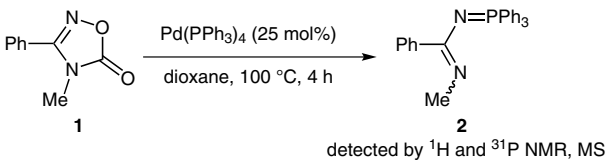
Key words: imidazoles, palladium, decarboxylation, aza-Wittig reaction

1,3-Diaza-heteroaromatic compounds, such as imidazoles and pyrimidines, are known as one of the most important classes of compounds, because they are commonly found in a variety of natural products and pharmaceuticals. Because of the basicity and coordination ability of imidazoles, they have been applied to functional materials, such as chemical sensors and biologically active molecules.[1] For several decades, much attention has been paid to the development of transition-metal-catalyzed synthesis of these heteroaromatics as novel or alternative methods.[2]

Recently, we have studied the transition-metal-catalyzed reactions of nitrogen-containing heterocyclic compounds involving nitrenoid species as intermediates. We have found that isoxazol-5(4*H*)-ones (isoxazolones) act as equivalents of vinylnitrene species under palladium catalysis (Scheme 1). Alkene-tethered isoxazolones efficiently underwent decarboxylative intramolecular aziridination by a palladium–phosphine catalyst to afford the corresponding fused aziridines (Scheme 1, a).[3] Isoxazolones also reacted with aldehydes in the presence of a palladium catalyst and a stoichiometric amount of triphenylphosphine (Ph_3P) to afford the 2-aza-1,3-dienes as products[4] through intermolecular aza-Wittig-type condensation (Scheme 1, b).[5,6] We thus expected that 1,2,4-oxadiazol-5(4*H*)-ones (oxadiazolones), possessing two nitrogen atoms in their heteroaromatic ring, would serve as iminonitrene precursors (Scheme 1, c).[7] Herein, we report an efficient synthetic method for imidazoles and pyrimidines using palladium-catalyzed decarboxylative condensation reactions of oxadiazolones bearing tethered carbonyl moieties (Scheme 1, c).



Scheme 1 Palladium-catalyzed decarboxylative transformation of nitrogen-containing five-membered molecules



Scheme 2

To confirm the generation of iminophosphorane species from oxadiazolones, the reactivity of a simple oxadiazolone toward a phosphine in the presence of a palladium catalyst was examined as an initial attempt. When a solution of oxadiazolone **1** and $Pd(PPh_3)_4$ (25 mol%) in dioxane was reacted at 100 °C for 4 hours, **1** was almost fully converted, and the generation of iminophosphorane **2** was detected by NMR and mass spectrometry (Scheme 2). The

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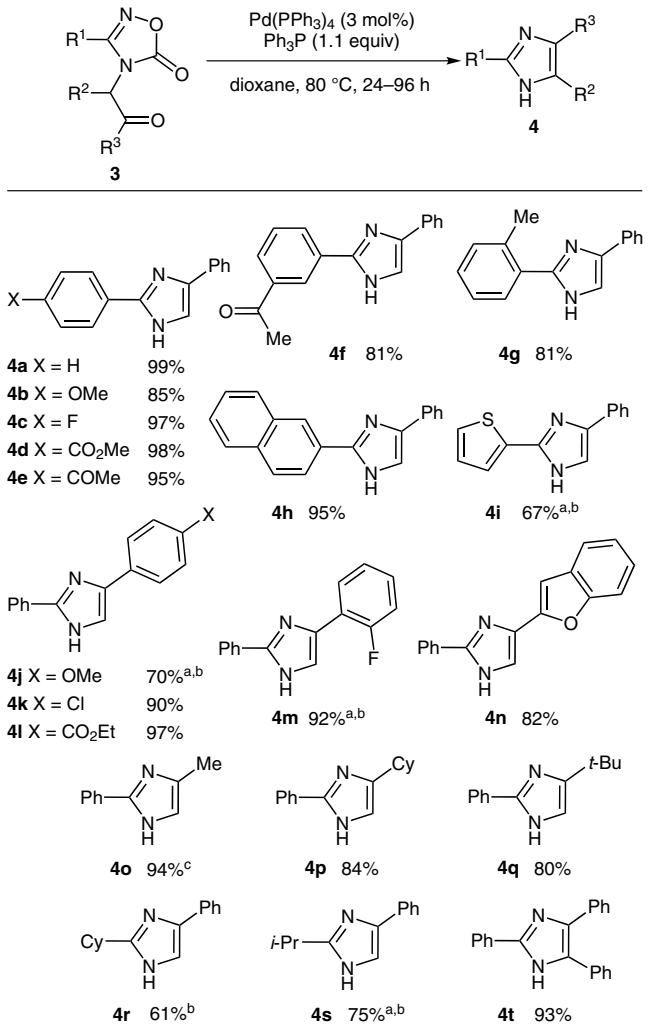
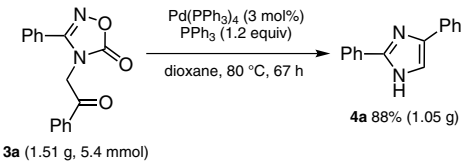
formation of **2** did not occur at all either in the absence of $Pd(PPh_3)_4$ or in the presence of only Ph_3P (without palladium), which indicates that iminophosphorane **2** was formed by the initial palladium-catalyzed decarboxylation of **1** followed by nitrene transfer from the generated nitrene–palladium species to Ph_3P.



Scheme 3 Palladium-catalyzed decarboxylative intramolecular aza-Wittig-type reaction of 1,2,4-oxadiazol-5-one **3** leading to imidazole **4**. The reactions were carried out with oxadiazolones **3** (0.20 mmol), $Pd(PPh_3)_4$ (3.0 mol%), and Ph_3P (1.1 equiv) in 1,4-dioxane (1.5 mL). Isolated yields are shown. [a] Conditions: 5 mol% of $Pd(PPh_3)_4$ were used. [b] At 100 °C. [c] $CpPd(\eta^3\text{-}C_3H_5)$ (3 mol%) and tppms (1.2 equiv) were used instead of $Pd(PPh_3)_4$ and Ph_3P.

As a result of various investigations of inter- and intramolecular condensation reactions, we were pleased to find that oxadiazolone bearing a ketone moiety (**3a**) underwent intramolecular condensation in the presence of 3 mol% of $Pd(PPh_3)_4$ and 1.1 equivalents of Ph_3P to afford the corresponding imidazole **4a** quantitatively. This imidazole-forming reaction also occurred effectively when oxadiazolones bearing various substituents were used (Scheme 3).[8] *para* Substituents on the aromatic ring R^1, such as methoxy, fluoro, acetyl, and methoxycarbonyl groups, did not affect the reaction efficiency (**4b**–**e**). A ketone moiety on the *meta* or *para* position remains intact during the reaction (**4e** and **4f**). *ortho*-Substituted phenyl, 2-naphthyl, and 2-thienyl groups could be employed as substituent R^1 (**4g**–**i**). Oxadiazolones bearing various aromatic groups (**4j**–**n**) as well as primary, secondary, and tertiary alkyl groups (**4o**–**q**) attached on the R^2 position are also applicable to the present reaction. Secondary alkyl groups were also compatible at the R^1 position (**4r** and **4s**). Triphenylimidazole (**4t**; $R^1 = R^2 = R^3 = Ph$) was also obtained in excellent yield.

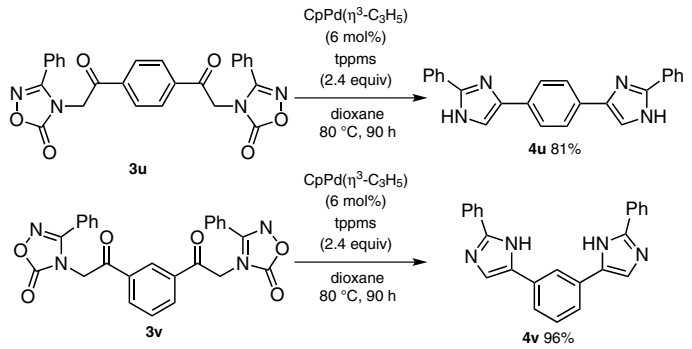
The present reaction was expanded successfully to the gram-scale preparation of imidazoles, and the standard palladium loading was enough for the formation of 1.05 g of imidazole **4a** in 88% yield (Scheme 4). Moreover, *meta*- or *para*-phenylene-bridged bis(imidazole) derivatives could be readily prepared using this method. Because triphenylphosphine oxide ($O{=}PPh_3$) was difficult to remove from the reaction mixture, we applied the conditions with the combination of $CpPd(\eta^3\text{-}C_3H_5)$ as a catalyst precursor and triphenylphosphanemonosulfonic acid sodium salt (tppms) as a condensation agent. The corresponding bis(imidazole) derivatives **4u** and **4v** were obtained in high yields (Scheme 5).



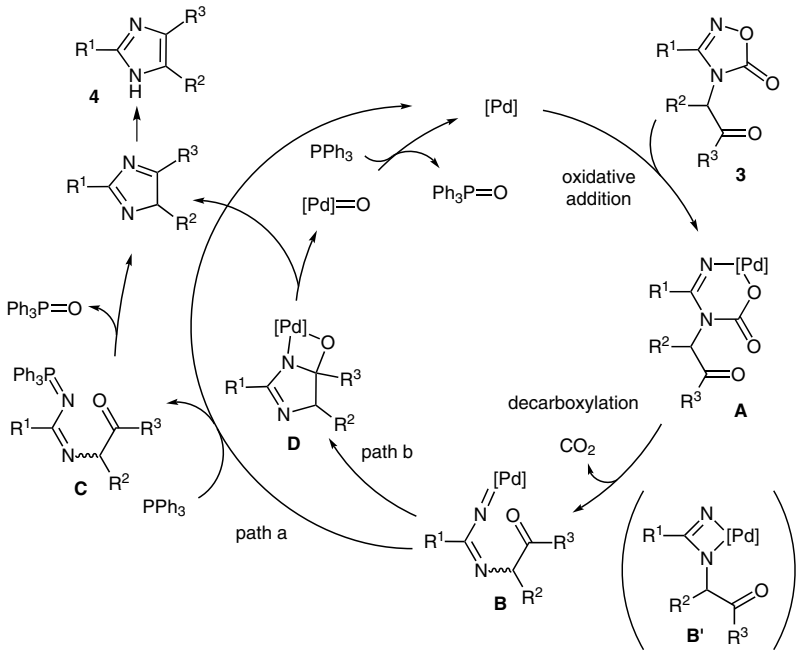
Scheme 4

A proposed catalytic cycle for the present reaction is shown in Scheme 6. First, oxadiazolone **3** oxidatively adds to the low-valent palladium species to form palladacycle **A**.[9–11] Decarboxylation from **A** generates the palladium–iminonitrene complex **B**.[12] Another possible active intermediate may be the four-membered diazapalladacycle **B′**. When enough Ph_3P exists in this system, iminophosphorane **C** is preferentially formed by fast nitrene transfer from intermediate **B** or **B′** to phosphine and undergoes intramolecular aza-Wittig-type condensation accompanied with isomerization to afford imidazole **4** and triphenylphosphine oxide (path a).[13,14] Unlike the intermolecular condensation reaction starting from isoxazolones, iminophosphorane species generated from the combination of phosphine and more electron-deficient nitrene species are considered to be much more stable because the iminophosphorane species could be detected in the reaction of simple oxadiazolone. Although the direct intramolecular cyclization of intermediate **B** without the formation of iminophosphorane **C** (path b) is also a possible alternative pathway, path a will be the major pathway compared with path b for the above reason.[15]

When we examined the reactivity of substrate **5**, in which the oxadiazolone moiety and the ketone moiety are linked with the vinylene tether, we found that the condensation reaction proceeds under similar conditions to form the

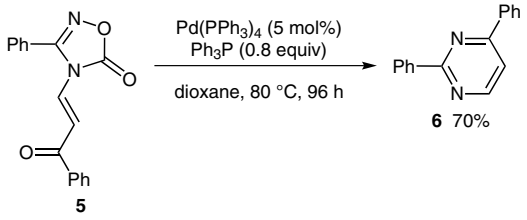


Scheme 5



Scheme 6 Proposed catalytic cycle for the palladium-catalyzed intramolecular condensation of oxadiazolone **3**

corresponding pyrimidine **6** in 70% isolated yield (Scheme 7). This result indicates the possibility that this reaction can be expanded to the general synthesis of various 1,3-diazaheterocyclic compounds.



Scheme 7

In conclusion, we have developed a palladium-catalyzed novel transformation reaction of readily available 1,2,4-oxadiazol-5(4*H*)-ones as starting materials with triphenylphosphine, leading to N-unprotected imidazole derivatives and a pyrimidine derivative. Because the present reaction proceeds under mild and neutral conditions, various functionalized imidazoles as well as bis(imidazole) derivatives could be obtained efficiently. Further investigations to improve efficiency in terms of catalytic activity and substrate scope are in progress.

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Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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(8) **General Procedure for the Catalytic Reactions**A solution of $Pd(PPh_3)_4$ (6.9 mg, 6.0 μmol) and oxadiazolone **3** (0.20 mmol) in 1,4-dioxane (1.5 mL) was stirred at 80 °C for 24 h. The reaction mixture was filtered through a pad of Florisil®, and the filtrate was concentrated under vacuum. The residue was subjected to column chromatography on Florisil® (hexane–EtOAc = 4:1) to afford imidazole **4**.

Imidazole 4a

White solid (43.8 mg, 0.20 mmol, 99% yield; mp 160.1–160.5 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.45 (m, 7 H), 7.75 (d, *J* = 7.4 Hz, 2 H), 7.87 (d, *J* = 7.3 Hz, 2 H). ^{13}C NMR (100 MHz, acetone-d_6): δ = 114.3, 125.4, 125.9, 127.2, 129.0, 129.3, 129.5, 131.8, 135.6, 142.6, 147.4. HRMS–FAB: *m/z* calcd for $C_{15}H_{13}N_2$ $[M + H]^+$: 221.1079; found: 221.1069.

Imidazole 4c

White solid (46.0 mg, 0.19 mmol, 97% yield; mp 65.0–66.1 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08 (dd, J_{HH} = 8.8 Hz, J_{HF} = 8.8 Hz, 2 H), 7.27 (t, *J* = 7.3 Hz, 1 H), 7.37 (s, 1 H), 7.39 (t, *J* = 7.3 Hz, 2 H), 7.74 (d, *J* = 7.3 Hz, 2 H), 7.82 (dd, J_{HH} = 8.3 Hz, J_{HF} = 4.9 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 115.7 (d, J_{CF} = 21.7 Hz), 117.7, 125.0, 126.4 (d, J_{CF} = 3.1 Hz), 127.2, 127.3, 127.5 (d, J_{CF} = 8.0 Hz), 128.8, 132.4, 146.7, 163.0 (d, J_{CF} = 248 Hz). HRMS–FAB: *m/z* calcd for $C_{15}H_{12}FN_2$ $[M + H]^+$: 239.0985; found: 239.0990.

Imidazole 4i

White solid (30.1 mg, 0.13 mmol, 67% yield; mp 168.5–171.0 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08 (dd, *J* = 5.1, 3.9 Hz, 1 H), 7.27 (t, *J* = 7.3 Hz, 1 H), 7.34 (d, *J* = 5.1 Hz, 1 H), 7.35 (s, 1 H), 7.39 (d, *J* = 8.1 Hz, 2 H), 7.41 (d, *J* = 3.7 Hz, 1 H), 7.72 (br s, 2 H). ^{13}C NMR (100 MHz, acetone-d_6): δ = 116.4, 124.1, 125.2, 126.3, 127.0, 128.2, 129.0, 134.4, 135.2, 140.5, 143.1. HRMS–FAB: *m/z* calcd for $C_{13}H_{11}N_2S$ $[M + H]^+$: 227.0643; found: 227.0639.

Imidazole 4j

Pale yellow solid (35.0 mg, 0.14 mmol, 70% yield; mp 124.3–126.2 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.84 (s, 3 H), 6.93 (d, *J* = 8.8 Hz, 2 H), 7.27 (d, *J* = 8.5 Hz, 2 H), 7.35 (t, *J* = 7.6 Hz, 1 H), 7.42 (t, *J* = 7.8 Hz, 2 H), 7.67 (d, *J* = 8.5 Hz, 2 H), 7.87 (d, *J* = 7.1 Hz, 2 H). ^{13}C NMR (100 MHz, acetone-d_6): δ = 55.3, 114.6, 125.7, 125.8, 126.6, 128.7, 129.3, 129.9, 131.1, 131.8, 146.9, 159.4. HRMS–FAB: *m/z* calcd for $C_{16}H_{15}N_2O$ $[M + H]^+$: 251.1184; found: 251.1181.

Imidazole 4o

White solid (29.7 mg, 0.19 mmol, 94% yield; mp 180.5–181.6 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 3 H), 6.82 (s, 1 H), 7.31 (t, *J* = 6.4 Hz, 1 H), 7.37 (t, *J* = 6.8 Hz, 2 H), 7.81 (d, *J* = 7.8 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.0, 119.4, 125.0, 128.2, 128.8, 130.4, 132.1, 146.0. HRMS–FAB: *m/z* calcd for $C_{10}H_{11}N_2$ $[M + H]^+$: 159.0922; found: 159.0923.

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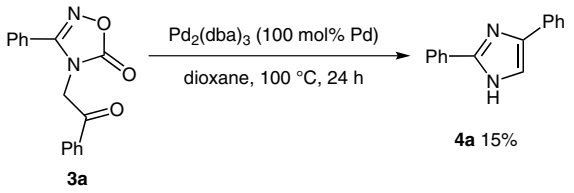

Scheme 8

