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# Assembly of 5-Aminoimidazoles via Palladium-Catalysed Double Isocyanide Insertion Reaction

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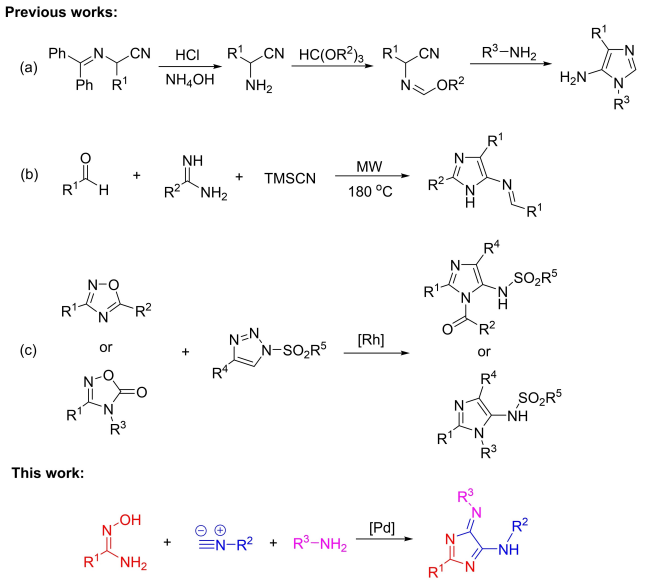
**Abstract:** A palladium-catalysed tandem cyclisation reaction of amidoximes, isocyanides and amines to produce 5-aminoimidazoles was developed. Various 5-aminoimidazoles were prepared in good to excellent yields under mild conditions. This elegant domino process involves the effective cleavage of the N–O bond and the formation of new C–C and C–N bonds in a single operation.

**Keywords:** Palladium-catalysed; Tandem cyclisation reaction; Isocyanide insertion; 5-Aminoimidazole derivatives

## Introduction

Imidazoles are an important class of heterocycles with wide applications in natural products,[1] pharmaceuticals[2] and materials.[3] Among functionally substituted imidazole derivatives, 5-aminoimidazoles have attracted increased attention owing to their excellent biological activities, such as Hsp90 inhibition,[4] adenosine $A_{2A}$ receptor antagonism[5] and antiplatelet[6] and antimicrobial activities.[7] Accordingly, great efforts have been devoted to the preparation of 5-aminoimidazole derivatives.[6,8–11] Multistep cascade reaction (Scheme 1a),[8] microwave-assisted multicomponent domino cyclisation (Scheme 1b)[9] and Rh-catalysed transannulation of 1,2,4-oxadiazoles with 1-sulfonyl-1,2,3-triazoles (Scheme 1c) are notable examples.[10] Despite this considerable progress, the syntheses of 5-aminoimidazoles are largely less developed, and they are often restricted by various drawbacks (e.g., tedious synthetic sequences, harsh synthesis conditions, special starting materials and use of expensive catalysts), which seriously limit their further applications. Therefore, the development of a more efficient protocol for synthesising 5-aminoimidazoles is highly desirable.

Isocyanides serve as highly versatile building blocks in organic synthesis owing to the carbene-like reactivity of their divalent carbon atom.[12] Palladium-catalysed isocyanide insertion reaction is a powerful route for constructing nitrogen-containing compounds.[13] Most methods involve aryl- or alkenyl-palladium species formation and sequential coupling with different nucleophilic partners to afford the target molecules. However, relatively few works have focused on multiple insertion of isocyanides.[14] In this regard, the exploration of novel palladium intermediates to merge with multiple isocyanide insertions is very important. Recently, we reported a palladium-catalysed multiple isocyanide insertion reaction to synthesise thiazole derivatives.[15] Inspired by this previous work and in continuation of our interest in the development of isocyanides,[16] we report herein a convenient approach for synthesising 5-aminoimidazoles from amidoximes, isocyanides and amines. This strategy enables effective assembly of 5-aminoimida-



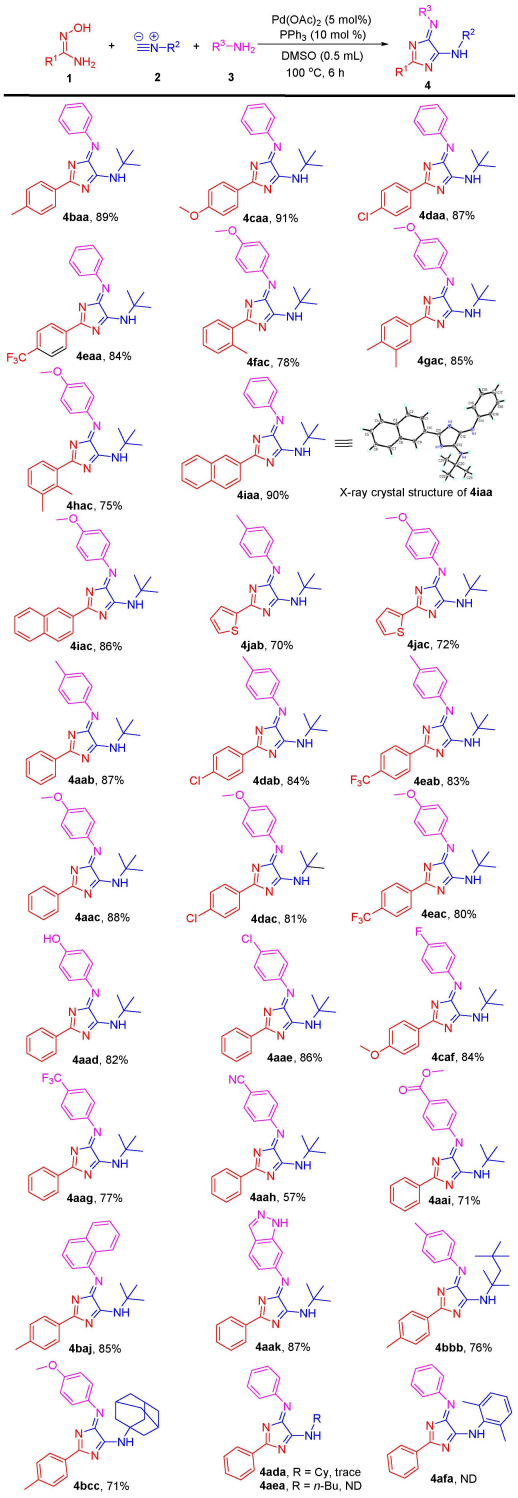

**Scheme 1.** Reported methods for the synthesis of 5-aminoimidazoles.

zoles through C–C and C–N bond formations and N–O bond cleavage.

Initially, *N*′-hydroxybenzimidamide (**1a**, 0.2 mmol), *tert*-butyl isocyanide (**2a**, 0.4 mmol) and amines (**3a**, 0.3 mmol) were used as model substrates to optimise reaction conditions (Table 1). Fortunately, the target compound **4aaa** was obtained in 47% yield with $PdCl_2$ (5 mol%) as catalyst, $PPh_3$ (10 mol%) as ligand in DMSO and sealed tube at 80 °C for 6 h (Table 1, entry 1). Subsequently, various palladium salts were tested, among which $Pd(OAc)_2$ provided the best result (Table 1, entries 2–7). In the absence of $PPh_3$, no product **4aaa** was detected (Table 1, entry 8). By contrast, poor results were achieved with $PCy_3$, $PMe_3$, $PBu_3$ and DPPP ligands compared with $PPh_3$ (Table 1, entries 9–12). Other solvents, such as DMF, NMP, DMA, toluene and 1,4-dioxane, also gave compound **4aaa** but in lower yields (Table 1, entries 13–17). When the reaction was conducted in DCE or $CH_3CN$, no **4aaa** was formed (Table 1, entries 18 and 19). Further investigation indicated that 100 °C was the most appropriate temperature, producing **4aaa** in 84% yield (entries 20–22). Notably, reducing the amount of solvent to 0.5 mL increased the yield of **4aaa** to 92% (entries 21 vs. 23).

However, reduction of $PPh_3$ to 5 mol% led to a sharp decrease in yield to 79% (Table 1, entry 24). Hence, **1a** (0.2 mmol), **2a** (0.4 mmol), **3a** (0.3 mmol), $Pd(OAc)_2$ (5 mol%) and $PPh_3$ (10 mol%) in DMSO (0.5 mL) and sealed tube at 100 °C were deemed as the optimised conditions.

Under the optimised conditions, various substituted amidoximes, isocyanides and anilines were examined

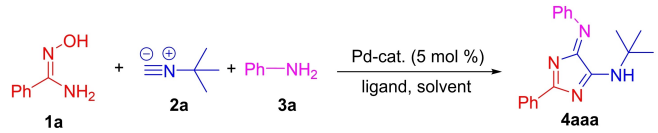



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), **3** (0.3 mmol), $Pd(OAc)_2$ (5 mol %), $PPh_3$ (10 mol %), DMSO (0.5 mL), at 100 °C, 6 h, sealed tube. [b]Isolated yields. ND = not detected.

**Scheme 2.** Synthesis of 5-aminoimidazoles **4**.[a,b]

(Scheme 2). Reactions with hydroxybenzimidamide containing electron-donating groups (e.g., 4-Me,

**Table 1.** Optimisation of reaction conditions.[a]




| Entry | Catalyst | Ligand | Solvent | Temp (°C) | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | $PdCl_2$ | $PPh_3$ | DMSO | 80 | 47 |
| 2 | $Pd(OAc)_2$ | $PPh_3$ | DMSO | 80 | 62 |
| 3 | $PdBr_2$ | $PPh_3$ | DMSO | 80 | 32 |
| 4 | $PdCl_2(PPh_3)_2$ | $PPh_3$ | DMSO | 80 | 45 |
| 5 | $Pd(acac)_2$ | $PPh_3$ | DMSO | 80 | 29 |
| 6 | $Pd(dba)_2$ | $PPh_3$ | DMSO | 80 | 26 |
| 7 | $Pd(PPh_3)_4$ | $PPh_3$ | DMSO | 80 | 52 |
| 8 | $Pd(OAc)_2$ | | DMSO | 80 | ND |
| 9 | $Pd(OAc)_2$ | $PCy_3$ | DMSO | 80 | 34 |
| 10 | $Pd(OAc)_2$ | $PMe_3$ | DMSO | 80 | 27 |
| 11 | $Pd(OAc)_2$ | $PBu_3$ | DMSO | 80 | 31 |
| 12 | $Pd(OAc)_2$ | DPPP | DMSO | 80 | 40 |
| 13 | $Pd(OAc)_2$ | $PPh_3$ | DMF | 80 | 50 |
| 14 | $Pd(OAc)_2$ | $PPh_3$ | NMP | 80 | 29 |
| 15 | $Pd(OAc)_2$ | $PPh_3$ | DMA | 80 | 43 |
| 16 | $Pd(OAc)_2$ | $PPh_3$ | toluene | 80 | 11 |
| 17 | $Pd(OAc)_2$ | $PPh_3$ | 1,4-dioxane | 80 | trace |
| 18 | $Pd(OAc)_2$ | $PPh_3$ | DCE | 80 | ND |
| 19 | $Pd(OAc)_2$ | $PPh_3$ | $CH_3CN$ | 80 | ND |
| 20 | $Pd(OAc)_2$ | $PPh_3$ | DMSO | 90 | 72 |
| 21 | $Pd(OAc)_2$ | $PPh_3$ | DMSO | 100 | 84 |
| 22 | $Pd(OAc)_2$ | $PPh_3$ | DMSO | 110 | 77 |
| 23[c] | $Pd(OAc)_2$ | $PPh_3$ | DMSO | 100 | 92 |
| 24[c,d] | $Pd(OAc)_2$ | $PPh_3$ | DMSO | 100 | 79 |

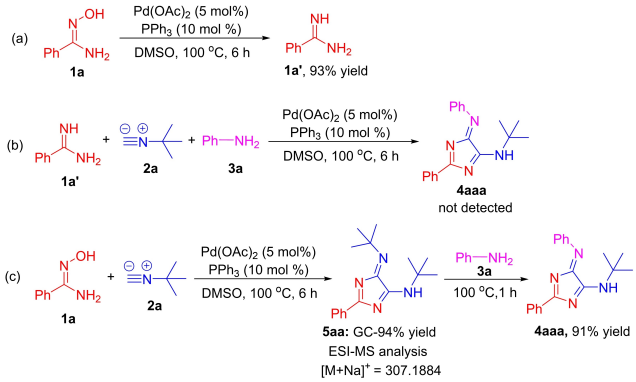
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), **3a** (0.3 mmol), Pd catalyst (5 mol%), ligand (10 mol%), solvents (1 mL), 6 h, sealed tube.
[b] Isolated yield of the pure product based on **1a**.
[c] Solvents (0.5 mL).
[d] ligand (5 mol%). ND = not detected.

4-OMe, 2-Me, 3,4-dimethyl and 3,2-dimethyl groups) and electron-withdrawing groups (e.g., 4-Cl and 4-$CF_3$) on the phenyl rings were well tolerated, obtaining the corresponding products (**4baa**–**4hac**) in good to excellent yields (75%–91%). The slightly lower yields of **4fac** and **4hac** were attributed to the *ortho* steric hindrance of the hydroxybenzimidamide. The naphthyl-substituted amidoxime was still effective at forming the desired products **4iaa** and **4iac** in 86% and 90% yields, respectively. The structure of **4iaa** was confirmed by X-ray crystal structure analysis (for details see the Supporting Information).[17] Furthermore, 2-thienyl-bearing amidoximes were found to be good substrates, affording the products **4jab** and **4jac** in 70% and 72% yields, respectively. We then investigated the substrate scope with respect to amines (**3b**–**3k**). Various anilines were compatible with the reaction conditions, delivering the desired products in moderate to good yields. Anilines **3b**, **3c** and **3d** possessing an electron-donating group, such as 4-Me, 4-OMe and 4-OH, at the aryl ring could lead to the target products **4aab**–**4aad** in 80%–88% yields, and some substrates bearing an electron-withdrawing group, including 4-Cl, 4-F 4-$CF_3$, 4-CN and 4-$CO_2CH_3$, at the benzene ring also performed smoothly and gave the desired products **4aae**–**4aai** in 57%–86% yields. Delightfully, 6-amino-1*H*-indazole (**3k**) could also be successfully transferred to the desired product **4aak** in 87% yield. Nevertheless, the alkyl amines were not applicable for this reaction under the current conditions, the alkyl amines presumably are not conducive to the amine exchange process Moreover, 1,1,3,3-tetramethylbutyl isocyanide (**2b**) and adamantyl isocyanide (**2c**) were tolerated in this transformation, affording the desired products **4bbb** and **4bcc** in 76% and 71% yields, respectively. Unfortunately, when the functional isocyanide **2d** was used, the product **4ada** was afforded in poor yield, and no desired products were detected when isocyanides

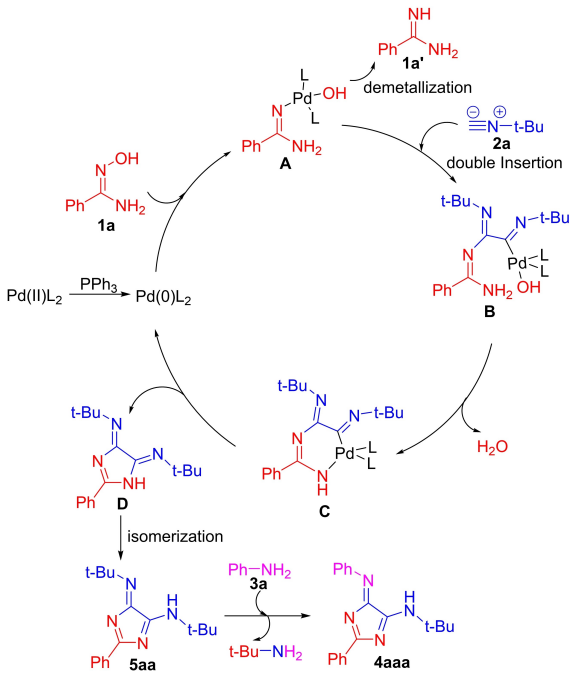
substituted with a primary alkyl group (**2e**) or an aryl group (**2f**) were used.

To demonstrate the synthetic utility of this reaction, we conducted the reaction in a gram-scale (Scheme 3). The multicomponent reaction could be easily scaled up to 4 mmol under the standard conditions, and the corresponding product **4aaa** was formed in 87% yield.


**Scheme 3.** Gram scale experiment.




**Scheme 4.** Control experiments.




**Scheme 5.** Possible reaction mechanism.

To probe the reaction mechanism, we performed several control experiments (Scheme 4). *N*′-Hydroxybenzenecarboximidamide (**1a**) was subjected to the optimised reaction conditions, and the compound benzamidine (**1a**′) could be isolated in 93% yield (Scheme 4a). However, when the reaction of benzamidine (**1a**′), tertbutylisonitrile (**2a**) and aniline (**3a**) was treated under standard conditions, no target product **4aaa** was observed (Scheme 4b), indicating that **1a**′ was not a possible intermediate of the transformation. We then conducted the reaction of **1a** with **2a** under standard conditions (Scheme 4c); (*Z*)-*N*-(*tert*-butyl)-4-(*tert*-butylimino)-2-phenyl-4*H*-imidazol-5-amine **5aa** ($[M+Na]^+ = 307.1884$) was detected in 94% GC-yield. Subsequently, **3a** was added, and the reaction mixture was heated at 100 °C for 1 h; the desired product **4aaa** was obtained in 91% yield, suggesting that **5aa** was an intermediate in the current reaction.

According to the above observations and previous reports,[14f,18] a plausible reaction mechanism for this transformation was outlined and depicted in Scheme 5. The first step is the formation of palladium species **A** via the oxidative addition of **1a** with $L_2Pd(0)$, followed by the double insertion of isocyanide **2a** to generate intermediate **B**, which can undergo cyclopalladation to give the palladacyclic complex **C**. Subsequent reductive elimination process in **C** lead to intermediate **D**. Isomerisation of intermediate **D** provides compound **5aa**. Eventually, the target product **4aaa** is obtained by an amine exchange process between aniline **3a** and **5aa**.

In conclusion, we discovered an efficient method for synthesising 5-aminoimidazole derivatives via palladium-catalysed multicomponent reactions involving isocyanide insertion. In view of this method's desirable features, such as readily available starting materials, operational simplicity, mild reaction conditions, moderate to excellent yields and good tolerance to scale-up synthesis, it is a powerful and appealing route for the rapid assembly of diverse 5-aminoimidazoles.

## Experimental Section

The reaction mixture of **1** (0.2 mmol), **2** (0.4 mmol), **3** (0.3 mmol), $Pd(OAc)_2$ (5 mol%), $PPh_3$ (10 mol%) and DMSO (0.5 mL) at 100 °C for 6 h in sealed tube was monitored periodically via TLC. Upon completion, the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with water and brine, dried over $Na_2SO_4$ and filtered. The solvent was removed under vacuum. The residue was purified by flash column chromatography to afford 5-aminoimidazole **4**.

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[17] CCDC 2058357 (**4iaa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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