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# Palladium-Catalyzed Double-Isocyanide Insertion via Oxidative N−O Cleavage of Acetyl Oximes: Syntheses of 2*H*-Pyrrol-2-imines

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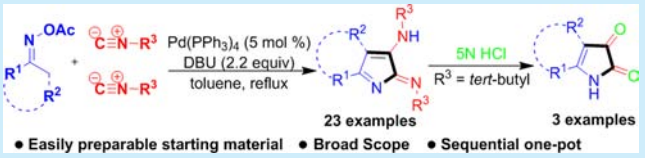
Supporting Information

**ABSTRACT:** The palladium-catalyzed reaction of acetyl oximes with isocyanides was developed for the synthesis of 2*H*-pyrrol-2-imines. The key steps were (i) generation of an enamido-palladium(II) species, (ii) migratory double-isocyanide insertion, and (iii) cyclization. The scope of the synthesis of some 2*H*-pyrrol-2-imines was extended to the synthesis 1*H*-pyrrole-2,3-dione/1*H*-benzo[*g*]indole-2,3-dione derivatives via acid hydrolysis in a sequential one-pot manner.

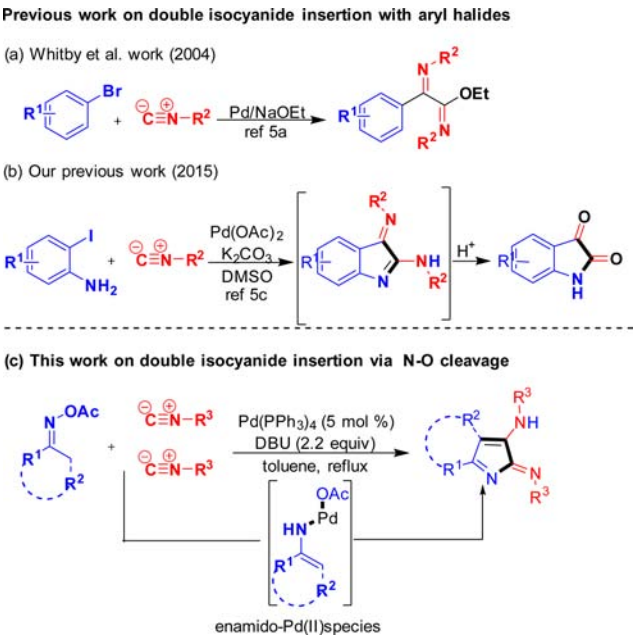



The 2*H*-pyrroles are important structural motifs of various biologically active compounds and natural products.[1] Among them, 2*H*-pyrrol-2-imines possess versatile applications in the field of applied chemistry.[2] For example, $BF_2$-chelated azadipyrromethanes (aza-BODIPY), a structural analogue of BODIPY, has been used as a photodynamic therapy agent,[2a,b] as a near-infrared fluorescent sensor,[2c−e] in selective metal-ion detection,[2f,g] and in electrochemical applications.[2h,i] The common methods to construct 2*H*-pyrrol-2-imines are from the condensation of *β*-benzoyl-*α*-phenylpropionitrile with hydroxylamine under acidic conditions[3] and from the reaction of *γ*-nitrobutyrophenone with ammonium acetate in protic solvent.[2a,h] Therefore, the development of 2*H*-pyrrol-2-imines with new functional groups in a simple and straightforward way will facilitate the ability for chemists to study their potential usefulness.

In recent years, metal-catalyzed single insertion of isocyanide has emerged as a powerful method for the construction of various heterocycles.[4] However, only a few examples of metal-catalyzed double-isocyanide insertion have been documented.[5] In particular, migratory double-isocyanide insertion via the oxidative addition of Pd(0) to Pd(II) was reported only with aromatic halides for the synthesis of nitrogen-containing compounds. For example, in 2004, Whitby et al. reported the synthesis of *α*-iminoimidates from aryl bromides in the presence of palladium catalyst (Scheme 1a).[5a] Later in 2015, we developed the synthesis of isatins from *o*-iodoanilines via the formation of 3-iminoindol-2-amines[5c,d] under palladium catalysis (Scheme 1b). Therefore, the development of new methods for the oxidative addition of isocyanides is still an interesting research area.

Oxidative addition of N−O bonds has been investigated in various Pd(0)/Pd(II)-catalyzed reactions for the synthesis of aza-heterocycles.[6,7] To the best of our knowledge, the concept of oxidative addition via N−O bond cleavage followed by isocyanide insertion has not been exploited. In continuation with our research on isocyanides,[5c,8] herein, we report an efficient method for the synthesis of 2*H*-pyrroles from acetyloximes and isocyanides under palladium catalysis. The reaction is assumed to proceed through the oxidative addition of oximes to Pd(0), generating an enamido-palladium(II) species, which is further trapped by isocyanides to form one C−N and two C−C bonds for the first time (Scheme 1c).

**Scheme 1. Previous and This Work on Double-Isocyanide Insertion via Oxidative Addition**

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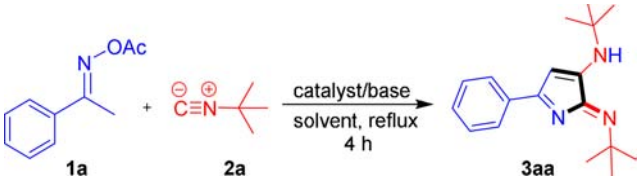
Our initial investigation began with (*E*)-1-phenylethan-1-one *O*-acetyl oxime **1a** and isocyanide **2a** as model substrates in the presence of 5.0 mol % of tetrakis(triphenylphosphine)-palladium(0), 2.2 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and acetonitrile (2.0 mL) as a solvent at reflux for 4 h, as shown in Table 1. However, the desired 2*H*-pyrrole derivative **3aa** was only obtained in trace quantities (Table 1). Subsequent reactions with other solvents such as 1,4-dioxane, THF, 1,2-DCE, DMF, chlorobenzene, benzene, and toluene (Table 1, entries 2–8) revealed that toluene under refluxing temperature gave the maximum yield of **3aa** at 86% yield (Table 1, entry 8). Other Pd(0) catalysts such as $Pd(dba)_2$ and $Pd_2(dba)_3$ did not improve the reaction yield of **3aa** (Table 1, entries 9 and 10). The reaction with an in situ Pd(0) catalytic system such as $Pd(OAc)_2/PPh_3$ also failed to improve the yield (Table 1, entry 11), and no product formation was observed with either $PdCl_2/PPh_3$ or $PdCl_2(PPh_3)_2/PPh_3$ (Table 1, entries 12 and 13). The effect of bases was tested with 1,4-diazabicyclo[2.2.2]octane (DABCO), pyridine, $Na_2CO_3$, $K_2CO_3$, $Cs_2CO_3$, and NaOAc (Table 1, entries 14–19). However, none of the bases resulted in an improved yield. Reducing the equivalents of DBU to 1.0 equiv reduced the yield of **3aa** to 42% (Table 1, entry 20), and in the absence of base, only a trace amount of product was observed (Table 1, entry 21). By replacing compound **1a** with (*E*)-1-phenylethan-1-one oxime or (*E*)-1-phenylethan-1-one *O*-methyl oxime as the substrate, the desired compound **3aa** was either isolated in 10% yield (Table 1, entry 22) or no product was formed (Table 1, entry 23). Thus, of the reaction conditions screened in Table 1, entry 8 was chosen as the optimum conditions.

**Table 1. Optimization of the Reaction Conditions**[a]

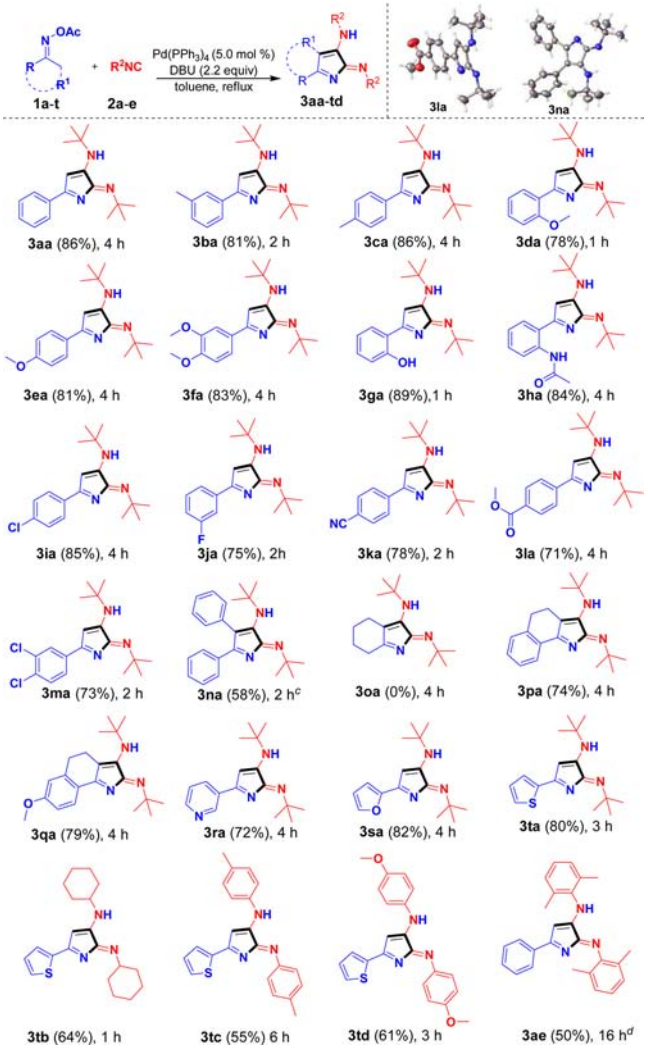



| entry | catalyst | base | solvent | yield (%)[b] |
|---|---|---|---|---|
| 1 | $Pd(PPh_3)_4$ | DBU | $CH_3CN$ | trace |
| 2 | $Pd(PPh_3)_4$ | DBU | 1,4-dioxane | 30 |
| 3 | $Pd(PPh_3)_4$ | DBU | THF | 40 |
| 4 | $Pd(PPh_3)_4$ | DBU | 1,2-DCE | 0 |
| 5[c] | $Pd(PPh_3)_4$ | DBU | DMF | 63 |
| 6 | $Pd(PPh_3)_4$ | DBU | PhCl | 40 |
| 7 | $Pd(PPh_3)_4$ | DBU | benzene | 65 |
| **8** | **$Pd(PPh_3)_4$** | **DBU** | **toluene** | **86** |
| 9 | $Pd(dba)_2$ | DBU | toluene | 62 |
| 10 | $Pd_2(dba)_3$ | DBU | toluene | 32 |
| 11[d] | $Pd(OAc)_2/PPh_3$ | DBU | toluene | 35 |
| 12[d] | $PdCl_2/PPh_3$ | DBU | toluene | 0 |
| 13[d] | $PdCl_2(PPh_3)_2/PPh_3$ | DBU | toluene | 0 |
| 14 | $Pd(PPh_3)_4$ | DABCO | toluene | <10 |
| 15 | $Pd(PPh_3)_4$ | pyridine | toluene | 0 |
| 16 | $Pd(PPh_3)_4$ | $Na_2CO_3$ | toluene | <10 |
| 17 | $Pd(PPh_3)_4$ | $K_2CO_3$ | toluene | <10 |
| 18 | $Pd(PPh_3)_4$ | $Cs_2CO_3$ | toluene | <10 |
| 19 | $Pd(PPh_3)_4$ | NaOAc | toluene | 0 |
| 20[e] | $Pd(PPh_3)_4$ | DBU | toluene | 42 |
| 21 | $Pd(PPh_3)_4$ | | toluene | trace |
| 22[f] | $Pd(PPh_3)_4$ | DBU | toluene | <10 |
| 23[g] | $Pd(PPh_3)_4$ | DBU | toluene | 0 |

[a]All reactions were carried out using **1a** (0.5 mmol), **2a** (1.05 mmol), catalyst (5 mol %), base (1.1 mmol), and solvent (2.0 mL) and stirred for 4 h at reflux temperature unless otherwise noted. [b]Isolated yield. [c]Reaction was performed at 110 °C. [d]Triphenylphosphine (20 mol %) was used. [e]DBU (1.0 equiv) was used. [f](*E*)-1-Phenylethan-1-one oxime was used instead of **1a**. [g](*E*)-1-Phenylethan-1-one *O*-methyl oxime was used instead of **1a**. The entry in bold represents the best conditions.

The scope and limitations of this methodology were investigated by screening acetyl oximes (**1a–t**) and isocyanides (**2a–e**) under standard conditions, as shown in Scheme 2. The reaction worked well with a series of R functionalities on the acetyl oximes such as *m*-Me-Ph (**1b**), *p*-Me-Ph (**1c**), *o*-MeO-Ph (**1d**), *p*-MeO-Ph (**1e**), 3,4-di-MeO-Ph (**1f**), *o*-OH-Ph (**1g**), *o*-acetamido-Ph (**1h**), *p*-Cl-Ph (**1i**), *m*-F-Ph (**1j**), *p*-CN-Ph (**1k**), *p*-COOMe-Ph (**1l**), and 3,4-di-Cl-Ph (**1m**). With the tertiary butyl isocyanide **2a**, these compounds reacted to afford the 2*H*-pyrrole

**Scheme 2. Scope and Limitations of Acetyloximes with Isocyanides To Synthesize 2*H*-Pyrrol-2-imine Derivatives**[a,b]




[a]Reaction conditions: compounds **1a–t** (0.5 mmol), **2a–e** (1.05 mmol), DBU (1.1 mmol) in toluene (2.0 mL) at refluxing temperature for indicated time unless otherwise noted. [b]Isolated yields. [c]Reaction was performed at 90 °C. [d]NMR spectra show two sets of –NH protons due to its resonance character.



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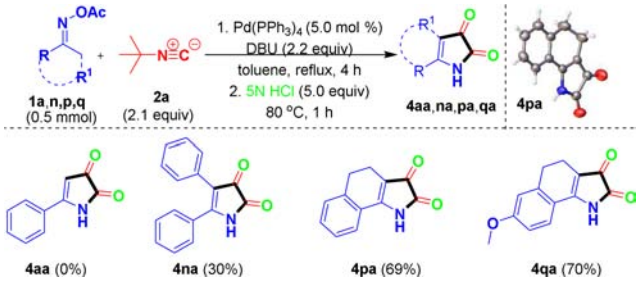
derivatives (**3aa**−**ma**) in 71−86% yields. The subsequent reaction of the $\alpha$-substituted derivative $\alpha$-Ph (**1n**) gave compound **3na** in moderate yield. The synthetic feasibility of cycloalkane derivatives such as cyclohexane (**1o**), $\alpha$-tetralone (**1p**), and 6-MeO-$\alpha$-tetralone (**1q**) gave the corresponding compounds **3pa**−**qa** in 74−79% yields, but the reaction failed to produce compound **3oa**. The scope of heteroaromatic acetyl oximes 3-pyridyl (**1r**), 2-furyl (**1s**), and 2-thiophenyl (**1t**) underwent smooth conversion to afford the bis-heterocyclic compounds **3ra**−**ta** in 72−82% yields. The structures of compound **3la** and **3na** were confirmed by X-ray analysis.[9] After the investigation of acetyl oxime derivatives, we evaluated the scope of the isocyanides **2b**−**e** with (*E*)-1-(thiophen-2-yl)ethan-1-one *O*-acetyl oxime (**1t**) and (*E*)-1-phenylethan-1-one *O*-acetyl oxime (**1a**), as shown in Scheme 2. The reaction underwent smooth conversion with cyclohexyl isocyanide **2b** to afford compound **3tb** in 64% yield. Subsequent reactions with the aromatic isocyanides such as 4-methyl phenyl isocyanide (**2c**), 4-methoxy phenyl isocyanide (**2d**), and 2,6-dimethyl phenyl isocyanide (**2e**) afforded the corresponding compounds **3tc**−**td** and **3ae** in 50−61% yields.

A brief literature survey revealed that 1*H*-pyrrole-2,3-dione derivatives are an important class of synthetic intermediates and can undergo a variety of transformations such as organocatalytic asymmetric reactions,[10] cycloadditions,[11] and nucleophilic addition reactions to build heterocycles.[12] Therefore, we extended the scope of this methodology to synthesize 1*H*-pyrrole-2,3-dione/1H-benzo[*g*]indole-2,3-dione derivatives through a sequential one-pot reaction via acid hydrolysis of the imino amine derivatives, as shown in Scheme 3.

**Scheme 3. Sequential One-Pot Reaction To Synthesize 1*H*-Pyrrole-2,3-dione/1*H*-Benzo[*g*]indole-2,3-dione Derivatives**[a]

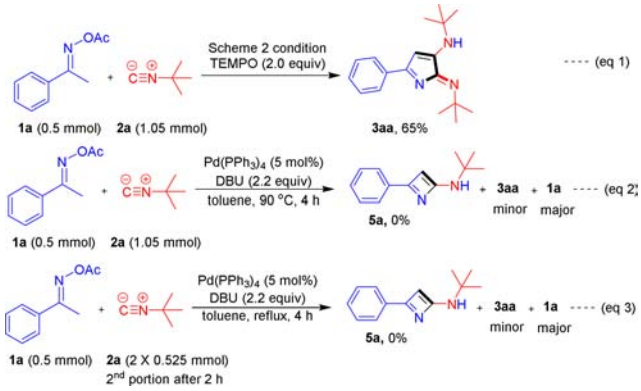



[a]Yields in the parentheses refer to isolated yields.

The preliminary reaction was tested with compound **1a** and isocyanide **2a** under the standard conditions presented in Scheme 2. After the formation of (*Z*)-*N*-(*tert*-butyl)-2-(*tert*-butylimino)-5-phenyl-2*H*-pyrrol-3-amine, the reaction was cooled to room temperature followed by the addition of 5 N HCl (5 equiv), and then, the reaction was heated for 1 h at 80 °C. However, the reaction failed to synthesize 1*H*-pyrrole-2,3-diones **4aa** due to the instability of **3aa** under acidic conditions. After a thorough investigation, we found that the 4,5-disubstituted derivatives of **3** were stable under acidic conditions for the hydrolysis reaction. The feasibility of the reaction was tested with $\alpha$-Ph (**1n**), $\alpha$-tetralone (**1p**), and 6-MeO-$\alpha$-tetralone (**1q**). To our surprise, the desired 2,3-dione derivatives **4na**, **4pa**, and **4qa** were isolated in 30−70% yields. The structure of compound **4pa** was confirmed by X-ray analysis.[9]

To understand the reaction mechanism, the control experiments shown in Scheme 4 were carried out. The reaction of **1a**

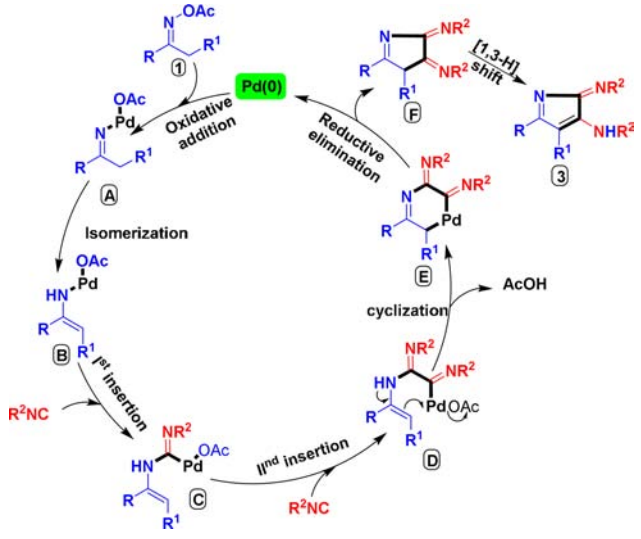
**Scheme 4. Experiments for Mechanistic Study**




and **2a** under the standard conditions in Scheme 2 in the presence of TEMPO gave **3aa** in 65% yield (Scheme 4, eq 1). This result ruled out the formation of a radical intermediate in the reaction. Next, the reaction was performed at lower temperature (eq 2) and with portionwise addition of tertiary butyl isocyanide **2a** (eq 3) to trap the iminoalkyl palladium(II) species generated through 1,3-Pd migration, as proposed by Stahl[7e] and Jiang.[7h] However, the expected single isocyanide inserted product was not obtained. Instead, a trace amount of compound **3aa** and recovered starting material were observed.

On the basis of previous studies[6,7e,h] and our observed results, we propose the mechanism shown in Scheme 5. Oxidative

**Scheme 5. Plausible Reaction Mechanism**




addition of acetyl oxime **1** to Pd(0) affords the palladium(II) species **A**, which can undergo tautomerization to produce the enamine-derived amido-Pd(II) species **B**.[7e] Because isocyanides have the ability to strongly coordinate to Pd(0), the migratory insertion can facilitate the generation of the imidoyl-Pd(II) species **C** rather than the 1,3-Pd migration. Intermediate **C** can undergo a second isocyanide insertion to afford the double-isocyanide insertion intermediate **D**. Then, intermediate **D** undergoes base-promoted cyclization to form the six-membered palladacyle intermediate **E**. Reductive elimination of **E** results in



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the formation of 2,4-dihydro-3*H*-pyrrol-3-imine intermediate **F** with the active regeneration of palladium(0) catalyst for the next catalytic cycle. A [1,3-H] shift[5c] of intermediate **F** results in the formation of the 2*H*-pyrrol-2-imine derivatives **3**.[13]

In summary, we have reported a new strategy for the insertion of double isocyanides through an oxidative N−O cleavage of acetyl oximes. The method was applied to the synthesis of 2*H*-pyrrol-2-imine heterocycles via one C−N and two C−C bond formations. The synthetic utility of some products was extended to construct 1*H*-pyrrole-2,3-dione/1H-benzo[*g*]indole-2,3-dione derivatives via a sequential one-pot reaction. Further applications of the 2*H*-pyrrol-2-imines are under investigation.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00208.

Experimental procedures, spectroscopic data and copies of NMR spectra for all new compounds (PDF)
X-ray crystallographic data for **3la** (CIF)
X-ray crystallographic data for **3na** (CIF)
X-ray crystallographic data for **4pa** (CIF)

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### Notes

The authors declare no competing financial interest.

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(13) An alternative mechanism is proposed in the Supporting Information, which involves a 1,3-Pd migration, double-isocyanide insertion, and amination to afford compound **3**.




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