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Rapid Syntheses of Heteroaryl-substituted Imidazo[1,5-a]indole and Pyrrolo[1,2-c]imidazole via Aerobic C2–H Functionalizations

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Abstract

Here we report an aerobic Pd(0) catalyzed C2–H functionalization of indoles and pyrroles with tethered N-methoxylamide as directing group. A Pd(0)-initiated mechanism overcomes the directing or poisoning effect from a wide range of heterocycles including pyridine, pyrimidine, and thiazole. The imidazo[1,5-a]indole products are transformed to bioactive analogs after one step manipulations, demonstrating the potential utility of this reaction in drug discovery.

Graphical Abstract

Imidazo[1,5-a]indole and pyrrolo[1,2-c]imidazole derivatives have been found to possess a wide range of biological activities (Figure 1). A number of applications in medicinal chemistry have been found by minor structural variations. For example, structure **a** could be used as light-dependent tumor necrosis factor- α (TNF- α) antagonists and antifungals.¹

Compounds containing structure **b** can serve as central nervous system (CNS) depressants,

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Notes

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Supporting Information

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Experimental procedures and spectral data for all new compounds (PDF).

analgesics and receptor antagonists.² Compounds **c** are aldose reductase inhibitors (ARI) and provide therapeutic possibility in the treatment of chronic complications in diabetes.³ Directed C2–H functionalizations of indole or pyrrole has been successfully exploited to synthesize these polycyclic heterocycles.^{4,5} Recently, Cui and others reported Rh(III)-catalyzed C2–H arylation using CONHOMe directing group⁵ previously developed in our laboratory.⁶ However, substrates containing heteroaryls are not described, presumably due to incompatibility. Considering the importance of heterocycles in drug discovery,⁷ it is crucial to develop catalytic systems that can functionalize heteroarylated indoles and pyrroles to provide synthetic routes for the preparation of heteroarylated imidazo[1,5-a]indole and pyrrolo[1,2-c]imidazoles.

Poor compatibility with heterocycles is a widespread problems in Pd-catalyzed C–H functionalizations. First, heterocycles could direct C–H activation at the undesired position; second, heterocycles could sequester Pd(II) catalyst via strong coordination and render them inactive. Three major approaches have been developed to overcome these undesired heterocycle effects. Masking the coordinating atom by strong acid or oxidizing the nitrogen to N-oxides have been employed for allylic C(sp³)–H of acetoxylation.⁸ Alternatively, the use of strongly coordinating bidentate directing groups can also circumvent this problem to some extent. Especially, the combination of bidentate oxazoline-based directing group and copper catalysts have demonstrated exceptional compatibility.⁹ The third approach involves design of directing groups that can coordinate with metal catalyst and also participate in subsequent bond forming event thereby outcompeting other heterocycles.¹⁰

We have previously developed a catalytic system in which Pd(0) is oxidized and sequestered by N-methoxyl amide directing group using air as the sole oxidant.^{10a} Pd(II)-coordinated with the amide directing group is rapidly trapped by isocyanide thereby overcoming interference from a wide range of heterocycles (a, Scheme 1). We wonder whether analogous transformation can be developed for C2–H functionalization of indole if *N*-methoxylamide group is tethered to indole via the urea linkage. If successful, a rapid synthetic route can be established for imidazo[1,5-a]indole derivative (b, Scheme 1). The anticipated compatibility of this reaction with heteroatoms might provide access to diverse imidazo[1,5-a]indole decorated with various heterocycles. Herein, we report an aerobic C2–H functionalization of indoles and pyrroles containing a wide range of heterocycles, which provides a new avenue to construct medicinally important imidazo[1,5-a]indole and pyrrolo[1,2-c]imidazole molecules.

We commenced the study with *N*-methoxy-1H-indole-1-carboxamide **1a** as the model substrate to explore the reaction. conditions. The proposed reaction could take place at 50 °C, affording the desired product **2a** in 60% yield, and the C3–H is intact.¹¹ However, 10% of byproduct **2a'** was also observed (entries 2–4, Table 1). In order to improve the selectivity of **2a** to **2a'**, reaction conditions were screened and it was found that concentration played an important role in the formation of **2a'**. Lower concentration led to lower yields of **2a'** and a slight improvement in the production of **2a** (entries 5–8, Table 1). When the concentration was less than 0.05 M, the yield of **2a'** could be reduced to lower than 5%. For the reason of practicability, we chose 0.04 M as the optimal concentration for further study (entry 9, Table 1).

With the reaction conditions established, it is crucial to examine the scope of indoles, especially the compatibility with heteroaryl-substituted indoles and pyrroles. *N*-methoxycarbonyl (MeONHCO-) protected 3-methylindole **1b**, 3-phenylindole **1c** and phthalimide protected L-phenylalanine methyl ester **1d** gave the corresponding products in moderate yields after a prolonged reaction time, which may be due to steric hindrance (**2b-2d**). Meanwhile, the moderate yield was obtained when scaled up the reaction to 1.0 mmol (**2a**, conditions b). 1-adamantyl isocyanide was also applicable in this reaction, affording **2a1** in 62% yield. Various electron donating and withdrawing substituents including methyl (**2m**, **2q**), methoxyl (**2g**, **2n** and **2r**), fluoro (**2i**), chloro (**2e**, **2j** (confirmed by X-ray) and **2p**), cyano (**2l**) and ester (**2g**, **2h**) at 4-, 5-, 6- and 7- position on indole were tolerated in this reaction, affording the desired products in moderate to good yields and excellent regioselectivity at C2 position (65%-80% yields). A relatively reactive bromo group was also well tolerated in this Pd(0) catalyzed reaction (**2k** and **2o**), which can serve as handle for further synthetic elaborations. Pyrrole was applicable in this reaction as well, furnishing product **2s** in 66% yield. When the C3 position of pyrrole was substituted with methoxycarbonyl group COOMe, C-H activation takes place at the less hindered C5 position exclusively in yield of 66% (**2t**). It is worth noting that 4- and 6-azaindoles **1u** and **1v** gave the corresponding products **2u** and **2v** in 61% and 42% yields respectively, demonstrating compatibility of heterocycles.

After exploring the generality with common indoles and pyrroles, we then extensively investigated the compatibility of heterocycles in this reaction (Scheme 3). In particular, we examined the presence of heterocycles that can potentially direct C-H activation at other sites leading to scrambling of regioselectivity. When pyridine was installed at C4 or C5 position of indoles, no detrimental effects were observed in this reaction. Importantly, no *ortho*-C-H activation directed by pyridine was observed with **3a-3c**. Pyrimidine, pyrazine and quinoline tethered at C5 position of indole were well tolerated, giving corresponding products in moderate to excellent yields (**4d-4f**). Substrates bearing five membered nitrogen containing heterocycles including pyrazole, oxazoline and thiazole at C5 position were well tolerated (**3g-3i**). The C-H bonds of electron-rich furan and thiophene can potentially be activated by Pd(II) in non-directed fashion to give undesired side products.¹² Under our standard conditions, the reaction produced the desired products **4j** and **4k** efficiently without side reactions occurring on the furan and thiophene rings. When the C3 position of pyrrole is substituted with a pyridyl group, C5-H was functionalized exclusively due to steric hindrance in 60% yield (**4l**). This result also suggests that the directing effect of pyridyl group is completely outcompeted.

Based on our previous mechanistic study on this catalytic system,^{10a} we propose a plausible mechanism for this reaction (Scheme 4). In the presence of air and **1a**, Pd(0) is oxidized to Pd(II) **A**, followed by 1,1-insertion of *t*-BuNC into the Pd-N bond to afford **B**. Acyl migration of **B** gives intermediate **C**, in which the C2-H is activated to give the six membered cyclopalladium(II) complex **D**. Reductive elimination of **D** furnishes the target product **2a** and releases active Pd(0).

To demonstrate the utility of the imidazo[1,5-a]indole products, a number of transformations were carried out. **2a** was converted to aforementioned bioactive molecules analogs through

simple manipulations (Scheme 5). The *N*-methoxyl imido group of **2a** was reduced to afford analogous CNS depressant **5a** under hydrogen with Pd/C as catalyst. When treated with sulfuric acid in methanol, the *N*-methoxyl imido group could be hydrolyzed to give dicarboximide **5b** in 66% yield. Switching solvent to tetrahydrofuran led to the removal of the *tert*-butyl group, affording 1H-imidazo[1,5-a]indole-1,3(2H)-dione **5b'**. Interestingly, reflux in trifluoroacetic acid can deprotect the *tert*-butyl group of **2a** selectively to give **5c** in 97% yield. Finally, treatment of **2a** with sodium hydroxide in mixed solvents of water and *n*-propanol furnished **5d** in nearly quantitative yield.

In summary, we have reported palladium(0) catalyzed isocyanide insertive C2–H functionalization of *N*-methoxycarbonyl protected indoles and pyrroles to afford imidazo[1,5-a]indole and pyrrolo[1,2-c]imidazole derivatives. This reaction is compatible with various functional groups. The amide directing group overrides directing or poisoning effect of diverse strongly coordinating heterocycles. The resulting imidazo[1,5-a]indoles could be transformed to bioactive analogs via simple synthetic manipulations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Representative bioactive compounds of imidazo[1,5-a]indole and pyrrolo[1,2-c]imidazole derivatives.

previous works:

this work:

Scheme 1.

Overcoming the Limitation of Heterocycle in $\text{Pd}(0)$ Catalyzed C–H Functionalizations.

Scheme 2. The Scope of indoles and pyroles.^a

^aReaction conditions: 0.2 mmol **1a–1l**, *t*-BuNC (2 equiv), $\text{Pd}_2(\text{dba})_3$ (5 mol %), 35 mL sealed vial, 60 °C, 10 h, isolated yields. ^b1.0 mmol scale. ^cWith 1-adamantyl isocyanide (2 equiv).

Scheme 3.

Overcome the limitation of heterocycles in C–H functionalization of indoles and pyrrole.^a

^aReaction condition: 0.2 mmol **3a-3l**, $t\text{-BuNC}$ (2 equiv), $\text{Pd}_2(\text{dba})_3$ (5 mol %), 35 mL sealed vial, 60 °C, 10 h, isolated yields.

Scheme 4.
Proposed mechanism for the formation of **2a**.

Scheme 5.
Transformations of Product 2a.

Optimization of Reaction Conditions.^{a b}

The reaction scheme shows compound 1a (a benzimidazole derivative with a methoxycarbonyl group) reacting with *t*-BuNC and Pd₂(dba)₃ in 1,4-dioxane to form products 2a and 2a'.

entry	temp/°C	V/mL	M/(mol/L)	2a	2a'
1	rt	1	0.1	trace	trace
2	50	1	0.1	60%	10%
3	60	1	0.1	66%	10%
4	70	1	0.1	64%	10%
5	60	0.5	0.2	49%	12%
6	60	2	0.05	66%	5%
7	60	3	0.033	66%	4%
8	60	5	0.02	69%	4%
9^c	60	5	0.04	70%^d	—

^aReaction conditions: 0.1 mmol **1a**, *t*-BuNC (2 equiv), Pd₂(dba)₃ (5 mol %), 15 mL sealed vial, 10 h.

^bYield determined by ¹H NMR analysis of crude reaction mixture using CH₂Br₂ as an internal standard;

^cWith 0.2 mmol **1a**, 35 mL sealed vial;

^dIsolated yield.