Synthesis of Phenanthridinones by Palladium-Catalyzed Cyclization of N-Aryl-2-aminopyridines with 2-Iodobenzoic Acids in Water

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Abstract The first Pd-catalyzed cyclization of N-aryl-2-aminopyridines with 2-iodobenzoic acids for the synthesis of phenanthridinones through C–H bond activation under very low catalyst loadings (down to 0.1 mol% Pd) in water is reported. This protocol features a broad substrate scope and provides easy efficient access to various phenanthridinones.

Key words phenanthridinones, palladium catalysis, cyclization, arylaminopyridines, iodobenzoic acids

Phenanthridinones, which consist of three fused six-membered rings, are frequently found in complex natural alkaloids and pharmaceutically active compounds exhibiting a broad range of biological activities, including antitumor, antiviral, anti-HIV, and DNA-topoisomerase-inhibitory activities.1 In recent decades, considerable efforts have been directed towards the synthesis of various phenanthridinones.2 Most of these approaches have focused on: (1) amide bond formation in 2′-aminobiphenyl-2-carboxylic esters or 2′-halobiphenyl-2-carbonitriles;3 (2) intramolecular C–C bond formation through annulation of N-(2-haloaryl)benzamides or C–H bond functionalization of N-arylbenzamides;4 (3) aminocarbonylative cyclization of o-arylanilines with CO, CO₂, or other carbonyl sources;5 (4) intramolecular C–H or C–halogen bond amidation of biaryl-carboxyamides;6 (5) radical-based decarboxylative cyclization7 and coupling reactions of aryl carboxamides with aryl iodides;8 (6) transition-metal-catalyzed coupling of N-substituted benzamides with aryl partners such as arenes,9 aryl halides,10 benzynes,11 aniline,12 aryl[(triethoxy)silanes,13 boronic acids,14 or others15 (Figure 1). Among these, the palladium-catalyzed direct functionalization of C–H bonds is an important synthetic tool for the synthesis of phenanthridinones. However, these routes suffer from such disadvantages as long reaction times, the need for inert atmospheric conditions, the necessity for large amounts of catalysts or complex ligands, and the use of toxic or volatile organic solvents. Although preparations of phenanthridinones at low catalyst loadings (1 mol% or 0.1 mol%) have been documented, the palladium pincer-type complexes used often required preparations involving multistep synthetic sequences.4h,14b Therefore, the development of an environmentally benign and cost-effective synthetic procedure is highly desirable from the viewpoint of green chemistry. Here, we report the first synthesis of phenanthridinones based on pyridinyl group-assisted palladium-catalyzed cyclization of N-aryl-2-aminopyridines with 2-iodobenzoic acids at very low catalyst loadings (down to 0.1 mol% Pd) in water.

To commence our studies, we selected N-phenyl-2-aminopyridine (1a) and 2-iodobenzoic acid (2a) as model substrates to optimize the reaction conditions. The reaction of 1a and 2a was first investigated in the presence of 0.1 mol% Pd(OAc)₂ as the catalyst and Ag₂CO₃ as an additive in water at 120 °C for three hours under an air atmosphere. Gratifyingly, the desired phenanthridine 3a was isolated in 85% yield (Table 1, entry 1). However, a sharp decrease in yield was observed in the absence of the additive (entry 2). On the basis of these encouraging results, several additives were evaluated, and Ag₂O was found to be the most suitable additive.

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for the transformation, giving the desired product 3a in 93% yield (entry 4). No further improvement of the yield was obtained on screening of other Pd(II) species (entries 9–11). A brief survey of solvents revealed that water was the optimal solvent, and the use of MeCN decreased the yield to 41% (entry 12). Other organic solvents EtOAc, THF, or toluene were found to be inferior and suppressed the reaction completely (entries 13–15). Finally, attempts to reduce the reaction temperature failed, resulting in a lower yield of 3a (entries 16 and 17). To demonstrate the possibility of large-scale operation, a scaled-up experiment at the 10 mmol scale was conducted and gave 3a in 85% yield (entry 18).

With the optimum reaction conditions in hand, we examined the scope and generality of the palladium-catalyzed cyclization of N-aryl-2-aminopyridines 1 with 2-iodobenzoic acid 2a (Scheme 1). A variety of N-aryl-2-aminopyridines bearing electron-donating (OMe, OPh) or electron-withdrawing substituents (F, Cl, Br, CF3, CN) in the para-, meta-, or ortho-positions of the phenyl ring were well tolerated and were converted into the corresponding products 3a–i in moderate to good yields. Note that electron-rich substrates tended to give relatively higher yields than did their electron-deficient counterparts. Moreover, disubstituted N-aryl-2-aminopyridines 1 were also suitable substrates, affording the desired products 3j–m in yields of 65–70%. In addition, a 1-naphthalene-derived precursor was successfully transformed into the product 3n in 78% yield. We then examined the effects of substituents on the pyridyl ring of the N-aryl-2-aminopyridines 1 and we found that substrates with Me or CF3 groups on the C3 or C5 position of the pyridine moiety reacted smoothly to furnish the desired phenanthridinone products 3o–q in yields of 55–63%. Notably, N-phenylquinolin-2-amine and N-phenylisooquinolin-1-amine were also compatible with the reaction conditions, giving products 3r and 3s, albeit in low yields.

We then tested the palladium-catalyzed cyclization protocol with a set of 2-iodobenzoic acids 2 (Scheme 2). Regardless of their electronic properties, steric hindrances, and substitution positions on the aromatic ring, the various 2-iodobenzoic acids 2 reacted smoothly to afford the corresponding phenanthridinones in medium to high yields. It is particularly noteworthy that sterically congested 2-iodo-3-methylbenzoic acid was an effective coupling partner, giving product 3u in 55% yield.

To further explore this reaction, we subjected N-(2-pyrimidyl)anilines and 2-iodobenzoic acid (2a) to the reaction conditions. However, the yields of the corresponding products 4a and 4b were markedly reduced, even with 10 mol% Pd catalyst loadings, possibly as a result of the poor coordinating ability of the pyrimidyl group. Moreover, simple diphenylamine (5) failed to deliver the desired product, highlighting the relevance of chelation assistance (Scheme 3).
Pd(OAc)₂ (0.1 mol%), Ag₂O (0.7 equiv), H₂O (1.0 mL), 3 h. The isolated yields are reported. (+) 

\[ \text{Scheme 1} \text{ Cyclization of N-aryl-2-aminopyridines 1 with 2-iodobenzoic acid (2a). Reagents and conditions: 1 (0.20 mmol), 2a (0.26 mmol), Pd(OAc)₂ (0.1 mol%), Ag₂O (0.7 equiv), H₂O (1.0 mL), 3 h. The isolated yields are reported.} \]

Finally, the pyridyl directing group was removed by a two-step quaternization/hydride-reduction process at room temperature to furnish phenanthridine-6-one (6) in an acceptable overall yield. (Scheme 4a). Some control experiments were also carried out to investigate the reaction mechanism. The attempted reaction of N-phenyl-2-amino pyridine (1a) with methyl 2-iodobenzoate and iodobenzene failed to give the desired products (Schemes 4b and 4c), suggesting that the carboxyl group plays a crucial role in this transformation. A subsequent reaction of the independently synthesized substrate 7 under the standard reaction conditions gave no product 3a (Scheme 4d), showing that no acylation of N-phenyl-2-amino pyridine (1a) by 2-iodobenzoic acid (2a) occurs in our transformation. However, treatment of the palladacycle dimer 17 with 2a in water at 120 °C for three hours resulted in the formation of the product 3a in 91% yield (Scheme 4e). 

\[ \text{Scheme 2} \text{ Cyclization of N-aryl-2-aminopyridines 1 with 2-iodobenzoic acids 2. Reagents and conditions: 1 (0.20 mmol), 2 (0.26 mmol), Pd(OAc)₂ (0.1 mol%), Ag₂O (0.7 equiv), H₂O (1.0 mL), 3 h. Isolated yields are reported.} \]

\[ \text{Scheme 3} \text{ Cyclization of N-(2-pyrimidyl)anilines or diphenylamine with 2-iodobenzoic acid (2a)} \]

\[ \text{Scheme 4} \text{ Protecting group removal and control experiments} \]
Based on our experimental results and previous studies, the tentative mechanism shown in Scheme 5 is proposed. The first step most probably involves coordination of Pd(II) to the nitrogen atom of the pyridine substrate; this is followed by a chelate-directed C–H activation to form the six-membered palladacycle dimer complex \( \text{I} \). Next, a carboxyl-mediated reductive elimination generates the ortho-arylated product 8, which undergoes intramolecular acylation to give 3a.

**Scheme 5 Proposed reaction mechanism**

In conclusion, we have developed the first palladium-catalyzed cyclization of \( N \)-aryl-2-aminopyridines with 2-iodobenzoic acids through C–H bond activation in water for the synthesis of phenantridinones. It is interesting to note that the reaction employs very low catalyst loadings (down to 0.1 mol\% Pd), and that water is the most effective solvent in this catalytic reaction. More mechanistic details and further studies on the scope of the substrates and applications of the reaction are currently being investigated in our laboratory.

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**Supporting Information**

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**References and Notes**


Phenanthridinones 3; General Procedure

Pd(OAc)\(_2\) (4.5 mg, 0.02 mmol) was dissolved in CH\(_2\)Cl\(_2\) (1 mL) and 10 \(\mu\)L of the solution was added to a Schlenk tube equipped with a Teflon-coated magnetic stirrer bar. The solvent was then evaporated under high vacuum. The appropriate N-aryl-2-aminopyridine 1 (0.20 mmol), 2-iodobenzoic acid 2 (0.26 mmol), and Ag\(_2\)O (32 mg, 0.14 mmol) were added to the Schlenk tube. Water (1.0 mL) was added, the tube was placed in a preheated oil bath (120 °C), and the mixture was stirred for 3 h. When the reaction was complete, the reaction tube was allowed to cool to r.t. and EtOAc was added. The organic layer was separated, and the azeous layer was washed with EtOAc. The filtrate was concentrated under reduced pressure, and the crude product was purified by flash column chromatography (silica gel).

5-Pyridin-2-ylphenanthridin-6(5H)-one (3a)

White solid; yield: 50 mg (93%); mp 185–186 °C. 1H NMR (400 MHz, CDCl\(_3\)) δ = 8.27–8.22 (m, 2 H), 7.97–7.93 (m, 1 H), 7.76–7.73 (m, 1 H), 7.57–7.53 (m, 1 H), 7.46–7.42 (m, 2 H), 7.28–7.21 (m, 2 H), 6.51 (d, \(J = 8.4\) Hz, 1 H). 13C NMR (100 MHz, CDCl\(_3\)) δ = 161.7, 151.9, 150.6, 139.3, 138.2, 134.2, 132.0, 128.1, 125.7, 124.8, 124.1, 123.1, 122.9, 121.9, 118.9, 116.4. HRMS (ESI-TOF): m/z [M + H]+ calcd for C\(_{18}\)H\(_{13}\)N\(_2\)O: 273.1028; found: 273.1036.

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