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Synthesis of 5-Aryl-5H-pyrido[2',1':2,3]imidazo[4,5-*b*]indoles by Domino Pd- and Cu-Catalyzed C–N Coupling Reactions

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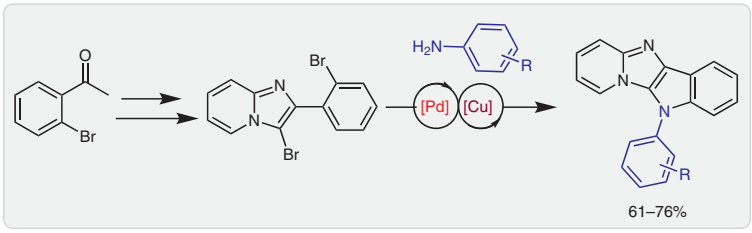

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Abstract A series of 5-aryl-5H-pyrido[2',1':2,3]imidazo[4,5-*b*]indoles was successfully prepared in good yields by a practical four-step strategy. In this procedure, the key step was demonstrated to be the domino Pd-and Cu-catalyzed C–N coupling reactions of 3-bromo-2-(2-bromophenyl)imidazo[1,2-*a*]pyridine with amines.

Key words fused N-heterocycles, C–N coupling, Pd catalysis, Ullmann reaction, domino reaction

Fused N-heterocycles constitute important targets in the drug discovery field.[1–4] In particular, indole moieties fused with other heterocycles have been evaluated and reported to show promising biological activities.[5–9] For example, indoloindoles **1**, benzofuroindoles **2**, and benzothioindoles **3** possess interesting activities against sexual hormone disorders as well as several types of cancer, because of their efficient antitumour capacity (Figure 1).[7–9] In addition, these structures have been useful in the treatment of congestive heart failure, asthma, irritable bowel syndrome, and cerebral vascular diseases.[6]

Imidazo[1,2-*a*]pyridine and its derivatives are present in many important drugs, such as the anxiolytics Alpidem,[10] Saripidem, Necopidem and in drugs of the Zolpidem family,[11] which are used for the treatment of insomnia and brain disorders. Their antiviral,[12,13] anti-inflammatory,[14,15] antibacterial,[16–18] analgesic, and antipyretic[14,19,20] properties have also been reported. Beyond the studies of imidazo[1,2-*a*]pyridines in medicinal chemistry, this structure has also found applications in materials science.[21–24] In fact, they exhibit interesting optical properties with high fluorescence quantum yields. Therefore, the combination of an imidazo[1,2-*a*]pyridine core with indole moieties to form the pyrido[2',1':2,3]imidazo[4,5-*b*]indole (PIDI) structure would give an interesting target to explore potential applications in drug discovery and materials science. The synthesis of pyrido[2',1':2,3]imidazo[4,5-*b*]indoles has gained much attention in recent years.[24] In 2012, Chauhan and coworkers developed a synthetic pathway to approach the PIDI structure by an isocyanide-based multicomponent Ugi reaction followed by Ullmann intramolecular cyclization (Scheme 1).[25] In order to avoid the employment of isocyanides, the Gryko group reported a four step pathway to prepare PIDI derivatives in moderate yields.[26] The key step in this synthesis was based on Cu-catalyzed C–H amination in the presence of PIDA as oxidant. Our group has developed

several synthetic methods to prepare highly fluorescent fused N-heterocycles (indoloindoles **1** and benzothioindoles **3**) relying on sequential site-selective Pd-catalyzed C–C and C–N reactions.[27,28] In this study, we continue to use our well-established methodology to prepare PIDI and its derivatives on the basis of domino Pd-, Cu-catalyzed two-fold double C–N coupling reactions. During the latter stages of preparation of this manuscript, Banerji et al. disclosed a similar approach to form PIDI structures with use of a Cu-catalyzed double C–N coupling reaction, employing $AgNO_3$ as the oxidant.[29] This report also described the highly fluorescent properties of the PIDI molecules and an interesting application in a live lysosome cell imaging study. Herein, we wish to report a practical four-step synthesis of PIDI molecules in very good isolated yields using cheap and readily available chemicals, involving a domino Pd-, Cu-catalyzed double C–N coupling route.

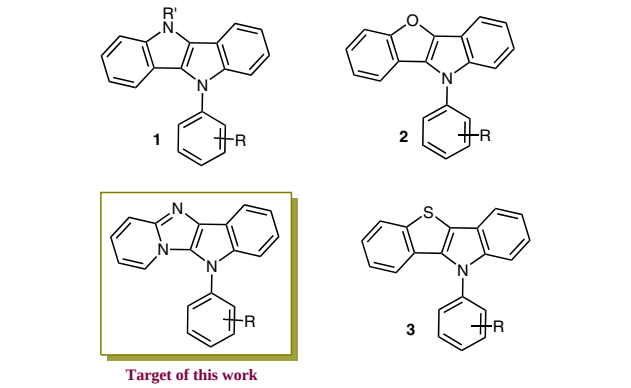
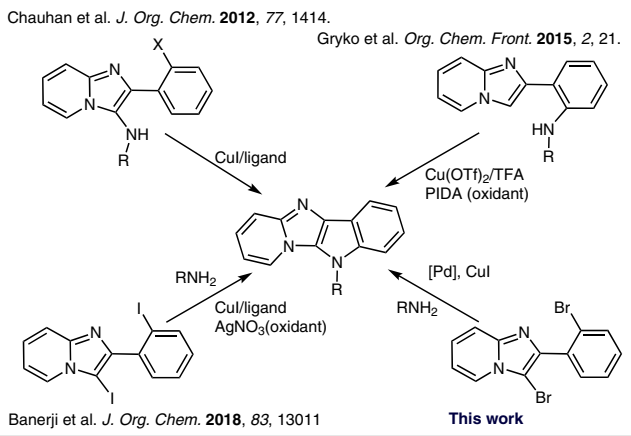
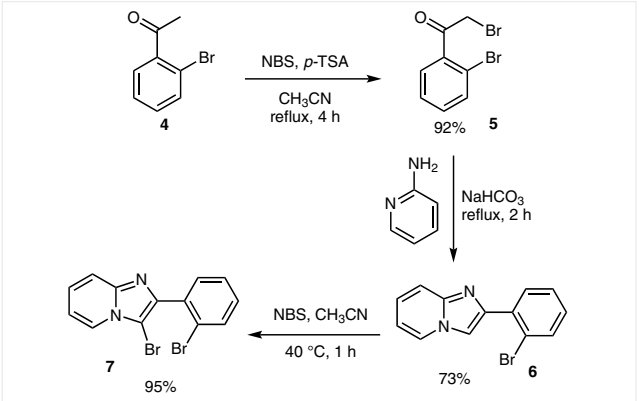


Figure 1 Several important fused N-heterocycles containing indole moieties



Scheme 1 Several reported approaches to the PIDI structure along with the current research

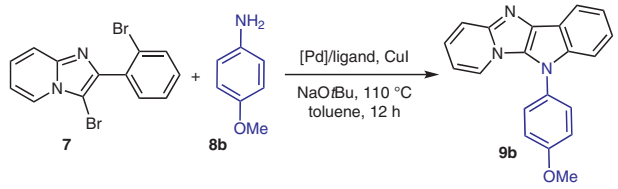
We started the synthesis using a well-known procedure reported by the Kumar group.[30] Brominated intermediate **6** was prepared by the cyclization of compound **5** with 2-aminopyridine in 73% yield. Regioselective bromination of compound **6** with NBS afforded our target key intermediate 3-bromo-2-(2-bromophenyl)imidazo[1,2-*a*]pyridine **7** in excellent isolated yield (95%, Scheme 2). Then, this compound (**7**) was used in a two-fold cyclization reaction with a range of amines to give our target molecules (Table 1).



Scheme 2 Synthesis of 3-bromo-2-(2-bromophenyl)imidazo[1,2-*a*]pyridine **7**

For the optimization of this key step, we chose the reaction of **7** with 4-methoxyaniline (**8b**) as the model reaction (Table 1). The employment of bidentate ligands in the combination of Pd precursors has been well established for C–N coupling. Therefore, we only focused on the screening of several common bidentate ligands in order to find the most suitable conditions for this transformation. Firstly, the standard conditions for C–N coupling using $Pd(OAc)_2$/BINAP (10 mol%/10 mol%) was applied but only 25% yield of desired product was obtained (entry 1). Then, we found that the use of $Pd_2(dba)_3$/BINAP (5 mol%/10 mol%) gave **9b** in 41% yield (entry 2). Further optimizations by using other bidentate ligands were unsuccessful and the mono C–N coupling compound was observed as the main side product. Relying on the previous report from the Chauhan group with use of a Cu catalyst, we decided to combine a Pd catalyst with a Cu catalyst in order to improve the yield of this reaction. After screening several Cu precursors in combination with different bidentate nitrogen ligands, we found that CuI (10 mol%) could be used as the co-catalyst for this reaction. Then, several bidentate ligands (dppe, dppf, DPEphos, Xantphos) were examined in combination with the CuI catalyst, and the Xantphos ligand appeared to be the most suitable ligand, leading to 84% yield of cyclized product (entry 6). The two common monodentate ligands PCy_3 and $P(tBu)_3$ for C–N couplings were investigated in this reaction, but only trace amounts of the desired product were observed by GC-MS. Various bases and solvents were also examined but did not give better yields (see Supporting Information). Similarly, variation of the reaction temperature (130 and 90 °C) did not result in better yields (see Supporting Information).

Table 1 Optimization of the Synthesis of PIDI **9b**[a]



Entry	Catalyst	Ligand	Co-catalyst	Yield (%)[b]
1	$Pd(OAc)_2$	BINAP	none	25[c]
2	$Pd_2(dba)_3$	BINAP	none	41[c]
3	$Pd_2(dba)_3$	BINAP	CuI	70
4	$Pd_2(dba)_3$	BINAP	$Cu(OAc)_2$	67[c]
5	$Pd_2(dba)_3$	BINAP	CuI/1,10-phenanthroline	60[c]
6	$Pd_2(dba)_3$	Xantphos	CuI	84
7	$Pd_2(dba)_3$	DPEphos	CuI	46
8	$Pd_2(dba)_3$	dppe	CuI	n.d.[d]
9	$Pd_2(dba)_3$	dppf	CuI	25
10	$Pd_2(dba)_3$	$PCy_3 \cdot HBF_4$	CuI	n.d.[d]
11	$Pd_2(dba)_3$	$P(tBu)_3 \cdot HBF_4$	CuI	n.d.[d]

[a] *Reaction conditions*: Compound **7** (0.28 mmol, 1.0 equiv), amine (0.43 mmol, 1.5 equiv), $Pd_2(dba)_3$ (5 mol%), ligand (10 mol%), CuI (10 mol%), NaO*t*Bu (1.70 mmol, 6 equiv), toluene, 110 °C, 12 h.
[b] Yield calculated by ^{1}H NMR spectroscopic analysis of the crude product by using 1,4-dioxane as an internal standard.
[c] The reaction mixture was complex and inseparable.
[d] Not detectable.

With the optimized conditions in hand,[31] we tried to explore the scope of the cyclization reaction of compound **7** with different aromatic amines (Table 2). The cyclized products were successfully synthesized in up to 76% isolated yield. The cyclization reaction of **7** with aniline only gave a moderate yield (62%). In general, the presence of electron-donating groups (OMe, SMe, *n*Bu) on the aromatic ring of the aniline resulted in higher product yields (**9b–g**) compared to the yields obtained with use of electron-withdrawing groups (F) (**9h**, **9i**). The structures of the products were confirmed by spectroscopic analysis. The structure of **9f** was confirmed by X-ray crystallographic analysis (Figure 2).

From the experimental results observed in Table 1, we concluded that the first site-selective Pd-catalyzed coupling reaction of **7** with anilines occurred at the imidazo[1,2-*a*]pyridine ring because of the chelating effect of the nitrogen atom. A large amount of uncyclized product was observed after the reaction. Prolonging the reaction time to 24 hours did not give a better yield of **9b**. In order to improve the yield of the desired product, CuI was introduced to the reaction as a co-catalyst in the second step (Ullmann-type reaction). Interestingly, product **9b** was obtained in 84% yield. Based on these results, we believe that the formation of cyclized products passes through a domino process that involves both Pd and Cu catalytic cycles (see Supporting Information).

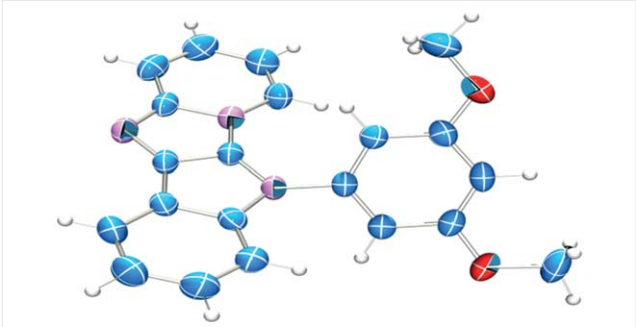
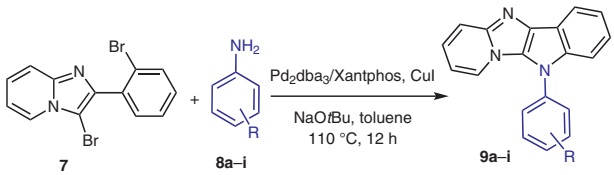


Figure 2 X-ray single-crystal structure of compound **9f** (CCDC number 1874276)

Table 2 Synthesis of PIDIs **9a–i**[a]



9	R	Yield (%)[b]
a	–	62
b	4-MeO	76
c	4-MeS	73
d	2,4-$(MeO)_2$	75
e	3,4-$(MeO)_2$	73
f	3,5-$(MeO)_2$	70
g	4-*n*Bu	68
h	4-F	65
i	3,4-F_2	61

[a] *Reaction conditions*: Compound **7** (0.28 mmol, 1.0 equiv), amine (0.43 mmol, 1.5 equiv), $Pd_2(dba)_3$ (5 mol%), Xantphos (10 mol%), CuI (10 mol%), NaO*t*Bu (1.70 mmol, 6 equiv), toluene, 110 °C, 12 h.
[b] Isolated Yield

In conclusion, we have disclosed a practical and convenient approach to the synthesis of a series of pyrido[2',1':2,3]imidazo[4,5-*b*]indoles in good yields. It is based on a new four-step strategy, in which the key step involves domino Pd-and Cu-catalyzed C–N coupling reactions. The advantage of our procedure is the avoidance of noxious isocyanide reagents as reported in previous studies. The results reported herein should be useful for potential applications in materials science and medicinal chemistry.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611957.

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(31) **Typical Procedure: Preparation of 5-Phenyl-5H-pyrido[2',1':2,3]imidazo[4,5-*b*]indole (9a)**
Aniline (40 mg, 0.426 mmol, 1.5 equiv) was added to a pressure tube that was charged with **7** (100 mg, 284 µmol, 1 equiv), $Pd_2(dba)_3$ (13 mg, 14 µmol, 0.05 equiv), Xantphos (16 mg, 28 µmol, 0.1 equiv), CuI (5 mg, 28 µmol, 0.1 equiv) and sodium *tert*-butoxide (164 mg, 1.7 mmol, 6 equiv) under argon. The tube was back-flushed with argon several times. Then, degassed anhydrous toluene (5 mL) was added under argon. The reaction mixture was heated at 110 °C for 12 h. After cooling, the reaction mixture was diluted with dichloromethane (20 mL), and the resulting mixture was filtered through a pad of Celite®, which was washed with dichloromethane (3 x 40 mL). The filtrate was concentrated in vacuo. The crude product was purified by flash chromatography (silica gel; hexane/dichloromethane/ ethyl acetate, 8:1:1) to yield **9a** (50 mg, 62%) as a yellowish solid. Mp 168–170 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.18–8.13 (m, 1 H), 7.77–7.70 (m, 2 H), 7.68–7.61 (m, 2 H), 7.58–7.55 (m, 1 H), 7.55–7.47 (m, 3 H), 7.33 (dd, *J* = 6.1, 3.1 Hz, 2 H), 7.11 (ddd, *J* = 9.3, 6.7, 1.4 Hz, 1 H), 6.70 (td, *J* = 6.7, 1.2 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 144.62, 141.03, 135.68, 131.37, 129.02, 128.38, 126.80, 125.53, 122.90, 121.40, 120.90, 120.13, 118.72, 117.89, 117.49, 109.90, 109.78. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{13}N_3$: 284.1188; found: 284.1190.