

A Simple and Efficient Synthesis of 2-, 3-, or 4-(2-Nitrophenyl)pyridine Derivatives via Palladium Catalyzed Ullmann Cross-Coupling Reaction

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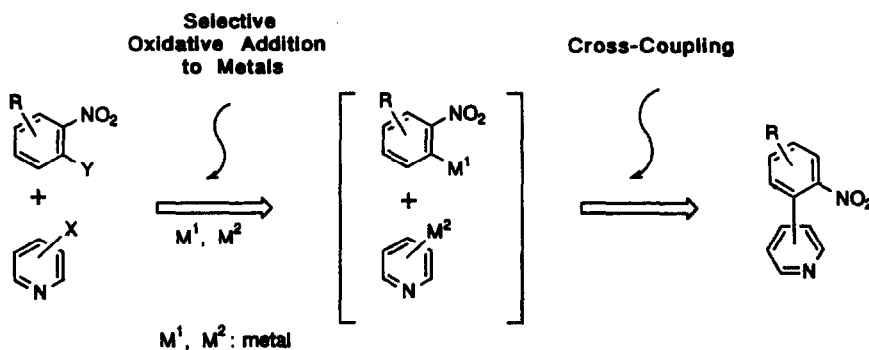
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Abstract: The Ullmann cross-coupling reaction of halopyridines with 2-bromonitrobenzenes was successfully catalyzed by low valent palladium [Pd(PPh₃)₄, PdCl₂(PPh₃)₂, PdCl₂] to afford (2-nitrophenyl)pyridine derivatives in good to excellent yield.

In search for potent antiarrhythmic active agents possessing the (2-substituted phenyl)pyridine framework,¹ we have been trying to develop an efficient method for preparing (2-nitrophenyl)pyridine derivatives,² which are used as key intermediates for the synthesis of these compounds. (2-Nitrophenyl)pyridine has conventionally been synthesized by the Gomberg-Bachmann-Hey reaction³ of 2-nitroaniline with pyridine or a palladium catalyzed cross-coupling reaction of diethyl(3-pyridyl)borane with 2-bromonitrobenzene (3a).^{4a} However, these processes are not satisfactory because regioisomers are formed and a strict condition is required for preparing the pyridylborane.^{4b} We now report a simple and efficient method of synthesizing (2-nitrophenyl)pyridine derivatives using a palladium catalyzed Ullmann cross-coupling reaction.⁵

As illustrated in Scheme 1, the construction of the phenylpyridine framework was based on the selective oxidative addition of halopyridine or 2-halonitrobenzene to two different metals, followed by the cross-coupling reaction.

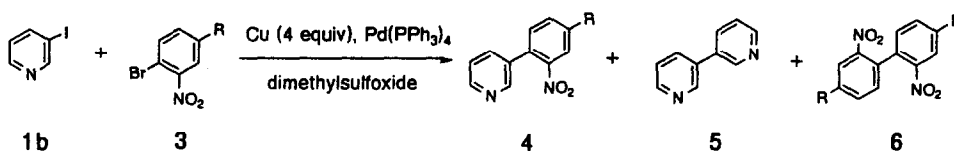
Scheme 1



^1H NMR analysis was performed to compare the relative reactivities of 3-halopyridines (halogen ; Br, I) and 2-halo-5-ethoxynitrobenzenes (halogen, Br, I) to a zero-valent palladium complex $\text{Pd}(\text{PPh}_3)_4$. Consequently, we found that the oxidative addition of 3-iodopyridine (**1b**) was faster than that of 2-bromo-5-ethoxynitrobenzene (**3d**).⁶ On the other hand, **3a** is highly reactive in the Ullmann reaction.⁷ Therefore, we selected copper and palladium as suitable metals to obtain the preferred oxidative addition of 2-bromonitrobenzenes (**3**) to copper in the presence of halopyridines, and the subsequent cross-coupling reaction between the two metal complexes.

Thus, we investigated a palladium catalyzed Ullmann cross-coupling reaction⁵ of **1b** with **3** (Table 1). A mixture of **1b**, **3** (2 equiv), copper bronze (4 equiv) and a catalytic amount of $\text{Pd}(\text{PPh}_3)_4$ in dimethylsulfoxide, stirred at 100 to 130 °C for several hours, gave the desired cross-coupling products **4** in high yields (entries 2 to 6). By contrast, this reaction of **1b** with **3d** without a palladium catalyst afforded the homo-coupling product **6** in a high yield (85%) and **4** in a low yield (12%) (entry 1). This indicates that the cross-coupling reaction between these two aryl halides in the presence of a palladium catalyst occurs selectively.¹¹

Table 1. Palladium(0) Catalyzed Cross-Coupling Reaction of **1b** with **3**




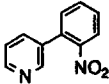

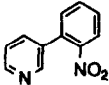

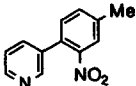

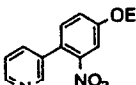

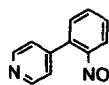

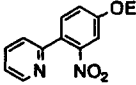

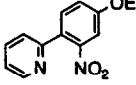
Entry	3 (2 equiv)	$\text{Pd}(\text{PPh}_3)_4$ (mol %)	Temp. (°C)	Time (h)	Yield(%) ^a of		
					4	5	6 ^b
1	3d (R=OEt)	—	100	2.5	12	7.5	85
2 ^c	3d (R=OEt)	5	100	5	78	1.0	56
3	3a (R=H)	5	130	1	90	5.7	54
4	3b (R=Me)	5	100	5	79	3.8	32
5	3c (R=OMe)	5	100	5	89	4.9	52
6	3e (R=OAc)	5	100	5	52 ^d	5.5	8.7 ^d

a. Isolated yields of pure products. b. Yields based on **3**. c. The reaction proceeded to give **4** in 80% yield using **3d** (1.2 equiv) and $\text{Pd}(\text{PPh}_3)_4$ (2 mol %), but was not optimized. d. Besides **4** and **6**, the deacetyl compounds of **4** and **6** were obtained in 30% and 5% yields, respectively.

Furthermore, this cross-coupling reaction was examined using $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ or PdCl_2 as a catalyst (Table 2). In the case of **1b** or 4-iodopyridine (**1c**), these reactions proceeded smoothly to give an

excellent yield of the corresponding cross-coupling products like the reaction using a zero-valent palladium catalyst (entries 1 to 5). However, in the case of 2-iodopyridine (1a), the reaction gave an unsatisfactory result (entry 6), which indicates that the oxidative addition of 1a to low-valent palladium and copper might occur non-selectively. On the other hand, the reaction of 2-bromopyridine (2) with 3d afforded the cross-coupling product in a good yield (entry 7).

Table 2. Palladium (II) Catalyzed Cross-Coupling Reaction of Halopyridines with 3^a

Entry	Halopyridine	3 ^b	Catalyst ^c (mol %)	Temp. (°C)	Time (h)	Cross-Coupling Product	Yield ^d (%)
1		3a	A (5)	130	1		94
2		3a	B (5)	130	1		92
3		3b	B (5)	100	2		94
4		3d	B (2)	100	2.5		90
5		3a	B (5)	100	2		86
6		3d	B (5)	100	1		29
7		3d	B (5)	120	1		47

a. All reactions were carried out in the same manner as in Table 1. b. 2 Equiv of 3 was used.

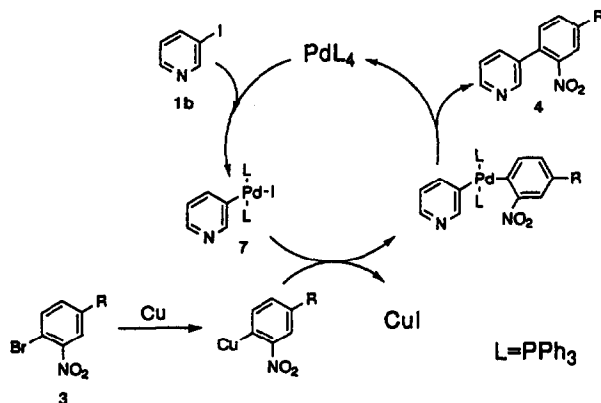
c. Catalyst A: PdCl₂(PPh₃)₂, Catalyst B: PdCl₂. d. Isolated yields of pure products.

In summary, a simple and efficient method of synthesizing (2-nitrophenyl)pyridine derivatives has been developed by using a palladium catalyzed Ullmann cross-coupling reaction, which proceeds in a highly chemoselective manner. From a preparative point of view, it is noteworthy that the most accessible and cheapest palladium compound PdCl₂ can be applied in the cross-coupling reaction. Further applications and limitations of this methodology are now being investigated.

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References and Notes

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- The typical experiment was done as follows. A mixture of equimolar amounts of 1b, 3d and Pd(PPh₃)₄ in dimethylsulfoxide-d₆ was heated at 100 °C for 40 minutes. After the reaction was completed, the product ratio of iodo(3-pyridyl)bis(triphenylphosphine)palladium(II) (7)^{8,9} to bromo(4-ethoxy-2-nitrophenyl)bis(triphenylphosphine)-palladium(II) (8)¹⁰ was estimated to be about 20 : 1 by the use of the integration values for the aromatic protons at δ 6.05 ppm (signal based on 7) and 6.61 ppm (signal based on 8).
- (a) Fanta P. E., *Synthesis*, 1974, 9. (b) Goshav M., Otroshchenko O. S. and Sadykov A. S., *Russian Chemical Reviews*, 1972, 41, 1046. (c) Fanta P. E., *Chem. Rev.*, 1964, 64, 613.
- 7: ¹H NMR (CDCl₃) δ 6.00 (1H, dd, J=7.8, 4.9Hz), 6.66 (1H, d quint, J=7.8, 1.5Hz), 7.90 (1H, d, J=1.5Hz); IR (KBr) 1476, 1431, 1091, 738, 689, 520 cm⁻¹.
- (a) Isobe K., Nakamura Y., Miwa T. and Kawaguchi S., *Bull. Chem. Soc. Jpn.*, 1987, 60, 149. (b) Isobe K. and Kawaguchi S., *Heterocycles*, 1981, 16, 1603.
- 8: ¹H NMR (DMSO-d₆) δ 1.20 (3H, t, J=6.8Hz), 3.73 (2H, q, J=6.8Hz), 6.50 (1H, dd, J=8.3, 2.4Hz), 6.61 (1H, d, J=2.4Hz), 7.14 (1H, dt, J=8.3, 2.4Hz); IR (KBr) 1502, 1432, 1250, 1093 cm⁻¹; mp 230-231°C.
- The probable reaction pathway is as follows. It is the key step in which the oxidative addition of 1b to Pd(PPh₃)₄ is faster than that of 3 in the presence of copper, followed by the preferential formation of 7. The subsequent reaction of 7 with the arylcopper produces the arylpyridylpalladium(II) complex, which undergoes 1,1-reductive elimination to yield 4 and regenerates a palladium(0) species.



- General reaction procedure: A mixture of halopyridine (1 mmol), 3 (2 mmol), copper bronze (4 mmol) and palladium catalyst (0.05 mmol) in dry dimethylsulfoxide (3 ml) was stirred at 100 to 130°C for 1 to 5h under nitrogen atmosphere. To the cooled reaction mixture was added 10% NH₄OH solution and CHCl₃, the mixture was stirred until copper dissolved. The mixture was filtered and the organic layer was separated, and then the aqueous layer was extracted with CHCl₃. The combined organic layers were washed with brine and dried (MgSO₄), and the solvent was evaporated. The products were purified by preparative thin-layer chromatography on silica gel or column chromatography on silica gel.
- All isolated compounds were identified by their IR, 270MHz ¹H NMR, and elemental analyses or mass spectra.

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