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Microwave-promoted synthesis of amino-substituted 2-pyridone derivatives via palladium-catalyzed amination reaction

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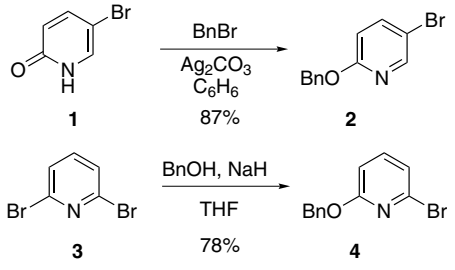
Abstract—A rapid and efficient synthesis of amino-substituted 2-pyridones was demonstrated by palladium-catalyzed amination reaction under microwave irradiation. This high-speed synthesis provided a number of amino-substituted 2-pyridones from the corresponding bromo-2-benzyloxypyridines via palladium-catalyzed amination followed by hydrogenolysis of benzyl ether.

A rapid and efficient synthesis of novel building blocks is still on tremendous demands in pharmaceutical and agrochemical research areas. In recent years, amino-substituted 2-pyridones have attracted attention due to their promising features as an important core structure for the development of biologically active molecules.[1] Pharmaceuticals with the 2-pyridone skeleton have emerged as antitumor,[2] antifungal,[3] antibacterial,[4] antiviral,[5] and antithrombotic[6] agents. Although many synthetic methods for the preparation of aminopyridine derivatives have been reported, there is still rare for the common preparation of amino-substituted 2-pyridones.[7] Therefore we envisioned that the palladium-catalyzed amination of bromopyridine with microwave irradiation would be utilized as a key step for the synthesis of amino-substituted 2-pyridones.[8,9] This microwave-promoted heating technology has become a powerful tool for the high-speed synthesis of novel chemical entities.[10] Many synthetic efforts using microwave were extensively focused on the amination of aryl bromides, chlorides, or triflates in the presence of a palladium catalyst.[11] Herein, we describe a convenient and efficient synthesis of a series of amino-substituted 2-pyridones via microwave-promoted palladium-catalyzed amination of 5- or 6-bromo-2-benzyloxypyridines followed by hydrogenolysis of benzyl ether.

The prerequisite 5- or 6-bromo-2-benzyloxypyridines were prepared by simple modifications of previous literature methods (Scheme 1). Selective *O*-benzylation was accomplished by the reaction of 5-bromo-2-pyridone **1** with benzyl bromide in the presence of silver carbonate in a dark to provide 2-benzyloxy-5-bromopyridine **2**.[12] On the other hand, 2-benzyloxy-6-bromopyridine **4** was easily obtained from 2,6-dibromopyridine **3** via mono-nucleophilic substitution with sodium benzyloxide in high yield.[13]

With bromopyridines in hand, we first carried out palladium-catalyzed amination of **2** with morpholine under microwave irradiation using conditions developed by Buchwald ($Pd_2(dba)_3$, (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP), NaO-*t*-Bu, and toluene).[14] It is well-known that the use of bis(phosphine) ligand such as BINAP is essential for the success of aminations of bromopyridines due to the formation of pyridine–palladium complexes.[14a]



Scheme 1.

Keywords: 2-Pyridone; Aminopyridine; Palladium-catalyzed amination; Microwave irradiation; Buchwald–Hartwig amination.
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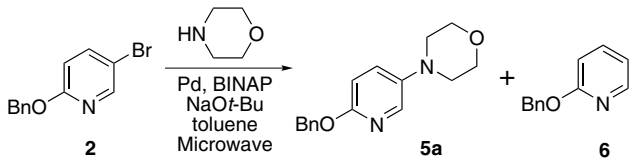
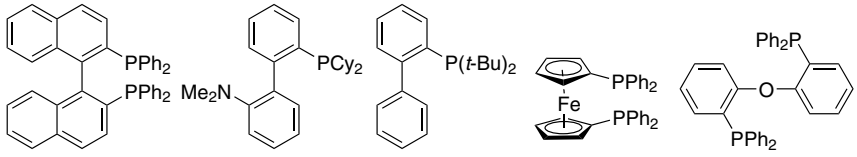
Table 1. Palladium-catalyzed amination of 2-benzyloxy-5-bromopyridine with morpholine[a]



2 5a 6

Entry	Pd source	Ligand[f]	Base	Temperature (°C)	Time (min)	Yield of **5a**[b] (%)
1	$Pd_2(dba)_3$	BINAP	NaO-*t*-Bu	150	10	65[c]
2	$Pd_2(dba)_3$	BINAP	NaO-*t*-Bu	150	5	80
3	$Pd(OAc)_2$	BINAP	NaO-*t*-Bu	150	5	50[c]
4	$Pd_2(dba)_3$	BINAP	NaO-*t*-Bu	130	10	81
5	$Pd_2(dba)_3$	BINAP	NaO-*t*-Bu	130	5	73[d]
6	$Pd_2(dba)_3$	BINAP	NaO-*t*-Bu	120	10	89
7	$Pd_2(dba)_3$	BINAP	NaO-*t*-Bu	80[e]	18 h	89
8	$Pd(OAc)_2$	BINAP	NaO-*t*-Bu	120	10	49[d]
9	$Pd_2(dba)_3$	BINAP	NaO-*t*-Bu	110	10	69[d]
10	$Pd_2(dba)_3$	**A**	NaO-*t*-Bu	120	10	90
11	$Pd_2(dba)_3$	**B**	NaO-*t*-Bu	120	10	52[d]
12	$Pd_2(dba)_3$	**C**	NaO-*t*-Bu	120	10	12[d]
13	$Pd_2(dba)_3$	**D**	NaO-*t*-Bu	120	10	14[d]
14	$Pd_2(dba)_3$	BINAP	Cs_2CO_3	120	10	15[d]
15	$Pd_2(dba)_3$	**A**	Cs_2CO_3	120	10	23[d]
16	$Pd_2(dba)_3$	**A**	K_2CO_3	120	10	14[d]
17	$Pd_2(dba)_3$	**A**	K_3PO_4	120	10	11[d]

[a] Reaction conditions: Pd (1 mol %), ligand (1.5 mol %), bromopyridine **2** (1 mmol), morpholine (1.2 mmol), base (1.4 mmol), toluene (3 mL).
[b] Isolated yield.
[c] Debrominated by-product **6** was detected (entry 3; 25%).
[d] Starting material **2** remained (entry 5; 7%).
[e] The reaction was performed under conventional oil-bath heating.
[f] Used ligands.



BINAP A B C D

As summarized in Table 1, microwave reaction in a sealed tube at 150 °C for 10 min provided the desired aminopyridine **5a** in 65% yield along with debrominated by-product **6** (entry 1). When carried out at 150 °C for 5 min, the reaction afforded the desired product in better yield (entry 2). As an alternative palladium source, the use of $Pd(OAc)_2$ under the same reaction conditions gave **5a** in 50% yield and the debrominated by-product **6** in 25% yield (entry 3). Based on these observations, $Pd_2(dba)_3$ is superior to $Pd(OAc)_2$ as the palladium source for the microwave-promoted amination reaction. To optimize microwave heating temperature, we continued to examine reactions at various temperatures and reaction times (entries 4–9). Decreasing reaction temperature to 130 °C for 10 min also gave **5a** in good yield (entry 4). However, shortening microwave exposure to 5 min at the same temperature resulted in lower yield (73%) due to the incompletion of the reaction (entry 5). When the reaction was run at 120 °C for 10 min, the best result was obtained to provide **5a** in 89% yield with all consumption of starting material (entry 6). This result was compatible with that of the conventional oil-bath heating conditions (entry 7). Further decreasing the reaction temperature to 110 °C led to lower yield due to incompletion of the reaction (entry 9). It is noteworthy that finely controlled reaction temperature and time (120 °C, 10 min) are critical factors for high yielding of the Pd-catalyzed amination of bromopyridine **2** under microwave irradiation.

Next, we examined several phosphine ligands and bases using the selected Pd-catalyst/temperature/time set. Of five phosphine ligands screened, BINAP and aminophosphine ligand **A** gave the best results (entries 6 and 10), while the reactions employing other ligands (**B**, **C**, and **D)** were incomplete (Table 1, entries 10–13). Base effects using Cs_2CO_3, K_2CO_3, or K_3PO_4 were clearly showed that the reaction progress became very slow and starting bromopyridne **2** remained significantly (Table 1, entries 14–17). Consequently, the optimum reaction set for the palladium catalyzed amination of bromopyridine is $Pd_2(dba)_3$, BINAP or ligand **A**, NaO-*t*-Bu at 120 °C for 10 min.

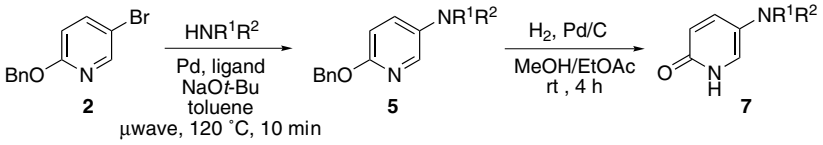
With the optimized conditions, we investigated the Pd-catalyzed amination of bromopyridine **2** with

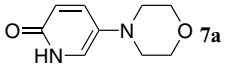
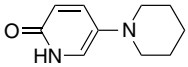
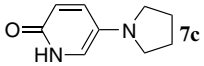
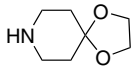
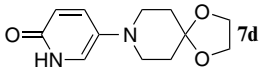
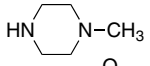
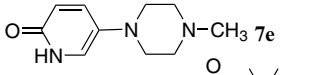
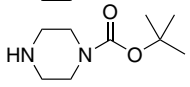
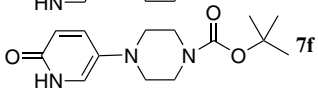
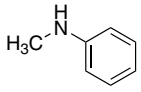
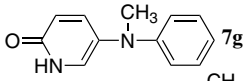
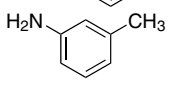
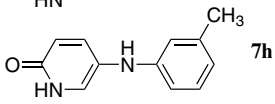
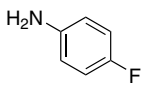
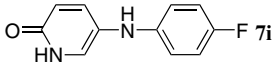
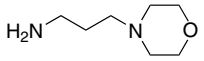
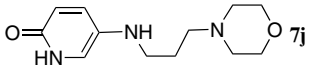
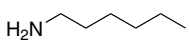
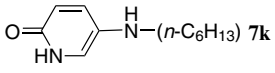
various amines to obtain amino-substituted pyridines **5**. The results are listed in Table 2.[15] In cases of cyclic secondary amines, amino-substituted pyridines **5a–f** were obtained in good to high isolated yields (entries 1–6). Aminations with aniline derivatives using BINAP or aminophosphine ligand **A** also furnished aminopyridines **5g–i** in good yields (entries 7–9). When aliphatic primary amines were used, the reactions were less effective, probably due to their ability of β-hydride elimination and dipyridinyl amination (entries 10–11).[14a,16] Finally, catalytic debenzylation of amino-substituted pyridines **5** was easily accomplished to provide the corresponding 2-pyridones **7a–k** in high yields (Table 2).

Further explorations of amination of 2-benzyloxy-6-bromopyridine **4** with some representative amines were carried out using the standard set developed. As outlined in Table 3, amination with cyclic secondary amines gave satisfactory results (entries 1–4). In cases of anilines and primary amines, amination was less effective and gave aminopyridines **8e–h** in moderate to good yields (entries 5–8). Then, catalytic debenzylation of aminopyridines **8a–h** was easily achieved to afford the corresponding 2-pyridones **9a–h** in high yields (Table 3).

In summary, we successfully demonstrated the simple and rapid synthesis of amino-substituted 2-pyridone derivatives using palladium-catalyzed amination under microwave irradiation. Such high-speed construction of 2-pyridone derivatives can be utilized to the discovery of useful pharmaceuticals. Further applications of palladium-catalyzed amination for the construction of novel building blocks are under investigation in our laboratory.

Table 2. Palladium-catalyzed amination of bromopyridine **2**[a] followed by hydrogenation[b]



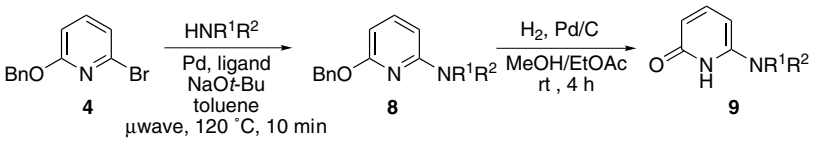
Entry	Amine	Ligand	Yield of **5**[c] (%)	2-Pyridone	Yield of **7**[c] (%)
1		**A**	90	 **7a**	92
2		BINAP	88	 **7b**	91
3		BINAP	69	 **7c**	92
4		BINAP	73	 **7d**	86
5		BINAP	85	 **7e**	95
6		BINAP	88	 **7f**	91
7		BINAP	72	 **7g**	92
8		**A**	89	 **7h**	90
9		**A**	78	 **7i**	95
10		**A**	71	 **7j**	89
11		**A**	60	 **7k**	90

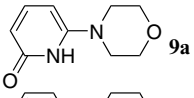
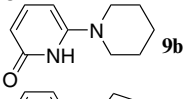
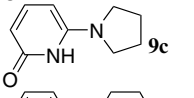
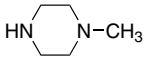
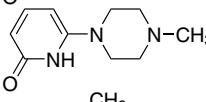
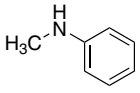
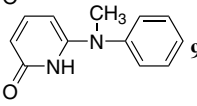
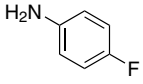
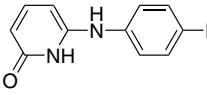
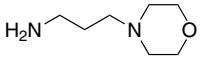
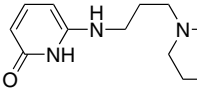
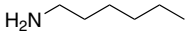
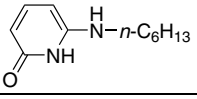
[a] Reaction conditions: $Pd_2(dba)_3$ (1 mol %), ligand (1.5 mol %), bromopyridine **2** (1 mmol), amine (1.2 mmol), NaO-*t*-Bu (1.4 mmol), toluene (3 mL), 120 °C, 10 min.

[b] Reaction conditions: H_2 (30–40 psi), 10% Pd/C (10 wt %), MeOH–EtOAc (2:1), 4 h.

[c] Isolated yield.

Table 3. Palladium-catalyzed amination of bromopyridine **4**[a] followed by hydrogenation[b]



Entry	Amine	Ligand	Yield of **8**[c] (%)	2-Pyridone	Yield of **9**[c] (%)
1		BINAP	80	 **9a**	95
2		BINAP	87	 **9b**	97
3		BINAP	92	 **9c**	92
4		BINAP	80	 **9d**	95
5		**A**	75	 **9e**	97
6		**A**	92	 **9f**	95
7		**A**	67[d]	 **9g**	80
8		**A**	65	 **9h**	85

[a] Reaction conditions: $Pd_2(dba)_3$ (1 mol %), ligand (1.5 mol %), bromopyridine **4** (1 mmol), amine (1.2 mmol), NaO-*t*-Bu (1.4 mmol), toluene (3 mL), 120 °C, 10 min.

[b] Reaction conditions: H_2 (30–40 psi), 10% Pd/C (10 wt %), MeOH–EtOAc (2:1), 4 h.

[c] Isolated yield.

[d] Dipyridinyl amine was detected by HPLC/MS (9%).

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15. *General procedure*: All amination reactions were conducted by using Biotage Initiator EXP™ microwave reactor. To a thick-well borosilicate glass vial (5 mL) was added bromopyridine (1 mmol), $Pd_2(dba)_3$ (1 mol %), BINAP (1.5 mol %) or aminophosphine **A** (1.5 mol %), amine (1.2 mmol), and NaO-*t*-Bu (1.4 mmol) sequentially. The mixture was dissolved in toluene (3 mL) and degassed with argon over 5 min. Then, the reaction vial was sealed and placed in the microwave reactor and irradiated at 120 °C for 10 min. After cooled to rt, the mixture was diluted with EtOAc and filtered through a short Celite pad. The solution was concentrated in vacuo and the residue was purified by silica gel flash column chromatography with EtOAc/hexanes as eluents to give aminopyridine **5**. Spectral data for **5a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, 1H, J = 2.9 Hz), 7.46–7.28 (m, 6H), 6.76 (d, 1H, J = 8.9 Hz), 5.33 (s, 2H), 3.87 (t, 4H, J = 4.7 Hz), 3.06 (t, 4H, J = 4.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.4, 142.5, 137.6, 134.2, 129.2, 128.4, 127.9, 127.7, 111.2, 67.6, 66.9, 50.5; MS (EI) m/z M^+ for $C_{16}H_{18}N_2O_2$ Calcd 270.14. Found 270.2 (9), 179.1 (21), 124.1 (17), 90.9 (100).
To a solution of aminopyridine **5** (1 mmol) in MeOH (4 mL) and EtOAc (2 mL) was added 10% Pd/C (10 wt %). The mixture was stirred for 4 h under hydrogen pressure (30–40 psi) and filtered through a short Celite pad. The solution was concentrated in vacuo and the residue was purified by silica gel flash column chromatography with MeOH/$CHCl_3$ as eluents to give 2-pyridone **7**. Spectral data for **7a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (dd, 1H, J = 9.7, 3.1 Hz), 6.87 (d, 1H, J = 3.1Hz), 6.59 (d, 1H, J = 9.8 Hz), 3.83 (t, 4H, J = 4.6 Hz), 2.88 (t, 4H, 4.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.1, 137.5, 135.0, 120.7, 120.2, 66.7, 51.0; MS (EI) m/z M^+ for $C_9H_{12}N_2O_2$ Calcd 180.09. Found 179.8 (23), 121.9 (48), 121.0 (49), 93.2 (29), 67.2 (25), 43.1 (100).
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