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Title

Intramolecular C–H arylation of pyridine derivatives with a palladium catalyst for the synthesis of multiply-fused heteroaromatic compounds

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Abstract

The C–H arylation of 2-quinolinecarboxyamide bearing C–Br bond at the N-aryl moiety is carried out with a palladium catalyst. The reaction proceeds at the C–H bond on the pyridine ring adjacent to the amide group in the presence of 10 mol% $Pd(OAc)_2$ at 110 °C to afford the cyclized product in 42% yield. The yield is improved to 94% when the reaction is performed with PPh_3 as a ligand of palladium. The reaction is examined with amides derived from unsubstituted picoline, 6-methyl-picoline, and 2,6-pyridinedicarboxylic acid in a similar manner to afford the cyclized product in 70%, 77%, 87%, respectively. The related reaction is also carried out with amides of non-pyridine derivatives terephthal- and benz- amides to afford multiply-fused heterocyclic compounds in 81% and 89% yields, respectively.

Keywords

Intramolecular C–H arylation; palladium acetate; phosphine ligand; pyridine amides; multiply-fused heterocycles

Introduction

Transition metal-catalyzed synthetic reactions have recently attracted much attention in synthetic organic chemistry [1,2]. C–H arylation reactions by the catalysis of a transition metal are of particular interest because the reaction involves rather superior efficiencies in atom economy [3,4]. The application of the reaction to an intramolecular manner represents a viable approach for the construction of several fused-ring skeletons [5]. Such ring structures containing heterocyclic rings would be of crucial importance because heterocycle-fused ring structures are found in a variety of advanced materials [6,7] and biologically important molecules [8–10]. A wide range of pyridine derivatives have been employed as an extractant of metal ions as a chelating agent [11]. Phenanthroline a class of the pyridine derivative has attracted attention for the efficient and selective extraction of lanthanides and actinides and, furthermore, a number of heterocycles involving pyridine rings have been reported to exhibit biological activities [12–20]. We have recently reported, as shown in Figure 1, that the introduction of a multiply fused structure toward a phenanthroline diamide (Phen-2,9-diamide) [21] employing the palladium-catalyzed intramolecular C–H arylation [22–26]. The reaction exhibits a remarkable extraction performance for a lanthanide ion, in which a metal specific extraction is found despite the periodic similarities in the lanthanides [21]. Chakravorty and co-workers reported that the similar arylation forms the fused skeleton in the bis-amide of 2,6-pyridinedicarboxlic acid (Py-2,6-diamide) [27]. Our interest has thus turned to extend the substrate scope of phenanthroline into

nitrogen-containing heteroaromatic compounds in the palladium-catalyzed C–H arylation. It is therefore intriguing to explore the possibilities of palladium-catalyzed intramolecular C–H arylation based on electronic rich/poor and steric hindered/less bulky demands. We herein report the palladium-catalyzed intramolecular C–H arylation of several pyridine and non-pyridine amides to afford multiply-fused heterocyclic compounds.

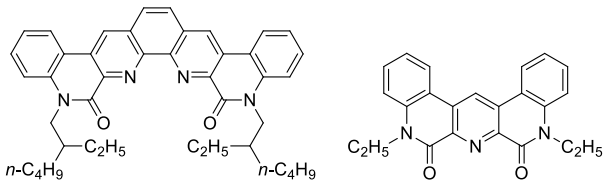
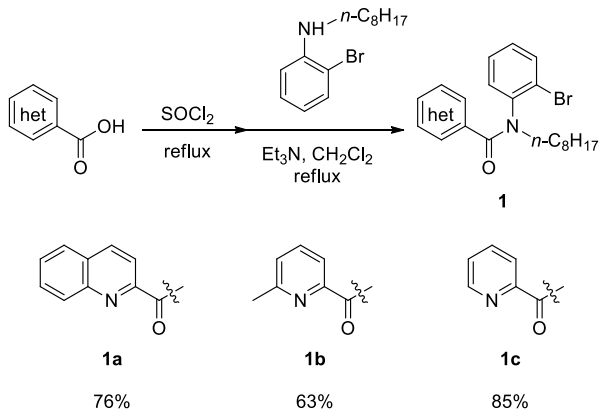


Figure 1. Structures of multiply-fused heterocyclic compound composed of pyridine rings

Results and Discussion

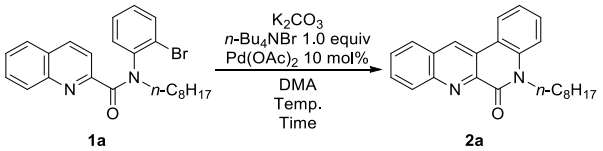
Synthesis of the cyclization precursors **1a**–**1c** was carried out by the reaction of the corresponding heteroaromatic carboxylic acid with thionyl chloride followed by treatment with *N*-octyl-2-bromoaniline [13]. The reaction proceeded smoothly to afford **1a**–**1c** in good yields as shown in Scheme 1.



Scheme 1. Synthesis of C–H arylation precursors

We first studied the reaction of quinoline amide **1a** under several conditions. We carried out palladium-catalyzed intramolecular coupling reaction of precursor **1a** under similar conditions [21], which underwent smooth reaction with phenanthroline bisamide, with 10 mol% of palladium acetate as a catalyst in the presence of potassium carbonate and tetra-*n*-butyl ammonium bromide in *N*,*N*-dimethylacetamide (DMA). Table 1 summarizes the results. The yield of the reaction improved as the temperature was increased from 90 °C to 130 °C (entries 1–3). When the reaction was carried out at 150 °C, the yield was decreased to 27%. A longer reaction period for 72 h at 130 °C also resulted in decreasing the yield to 27% (entries 4, 5). It was found that the use of the increased amount of potassium carbonate to three fold excess improved the yield of **2a** to 59% in the reaction at 110 °C shown in entry 6. The effect of the ligand of the palladium catalyst was then examined. The addition of ligand improved the yield of **1a** as shown in entries 7–10. Among several ligands including Buchwald-type phosphines [28] examined, it was found that the use CyJohnPhos afforded the cyclized product in 90% yield and the reaction with PPh_3 as a ligand was also effective to afford **2a** in 94% yield.

Table 1. Studies on the reaction conditions for **2a** from **1a**



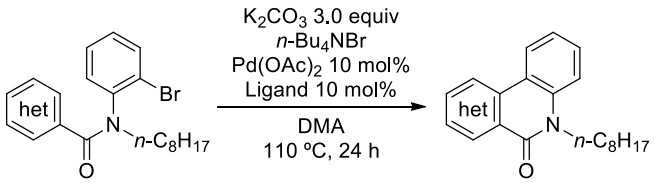
Entry	Temp. (°C)	K_2CO_3 (equiv)	Time (h)	Ligand	Yield (%)[a]
1	90	1.0	24	none	7[b]
2	110	1.0	24	none	42
3	130	1.0	24	none	49
4	150	1.0	24	none	27
5	130	1.0	72	none	27[b]
6	110	3.0	24	none	59
7	110	3.0	24	SPhos[c]	58
8	110	3.0	24	PCy_3[d]	69
9	110	3.0	24	CyJohnPhos[e]	90
10	110	3.0	24	PPh_3	94

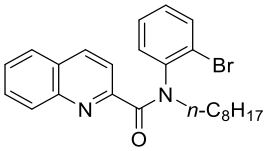
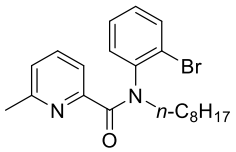
[a]Yield determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as an internal standard; [b]isolated yield; [c]SPhos = 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl; [d]PCy_3 = tricyclohexylphosphine; [e]CyJohnPhos = 2-(dicyclohexylphosphino)biphenyl.

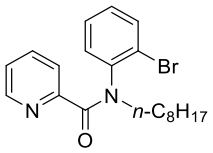
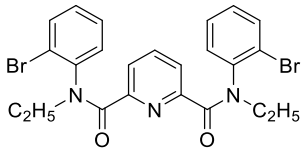
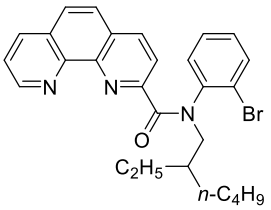
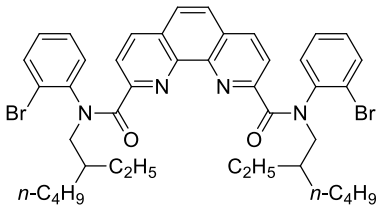
The reaction was carried out with several pyridine derivatives as summarized in Table 2. The reaction was compared with an amide derivative composed of 6-methylpicoline (**1b**), unsubstituted picoline (**1c**), etc. When the reaction was examined in the absence of a phosphine ligand, the yields of the cyclized product were much worse than the reaction of **1a** resulting that the yield of **2b** decreased to 18% and that of **2c** to 5%. The use of PPh_3 as a ligand slightly improved the yield to 58% and 24%, respectively. The highest yield of **2b** was obtained in the use of CyJohnPhos, while

PCy_3 (tricyclohexylphosphine) resulted in giving the best yield in the reaction of **1c**. Concerning the reaction of **1c**, the use of tetra-*n*-butyl ammonium bromide and pivalic acid as additives and PCy_3 as a ligand further improved the yield to 77%. Chakravorty and coworkers showed that a smooth reaction proceeded with pyridine 2,6-dicarboxylic acid bisamide **1d** [27]. We thus compared the reaction of **3** under similar conditions to that of **1a** and the reaction afforded **4** in 87% yield, which was found to be comparable with the case of **1a**. The reactivity toward the palladium-catalyzed cyclization was thus shown as **3** ≈ **1a** >> **1b** > **1c**. The related trend was also observed in the reaction of phenanthroline monoamide **5a** and diamide **5b**. The reaction of **5a** afforded the cyclized product in 51% yield, which contrasted with our previous result for the cyclization of **5b** to afford the doubly cyclized product **6b** (reported yield: 85% [21]), suggesting that the superior reactivity was found in bifunctional bisamide to monoamide.

Table 2. Pd-catalyzed C-H arylation of heteroarenes



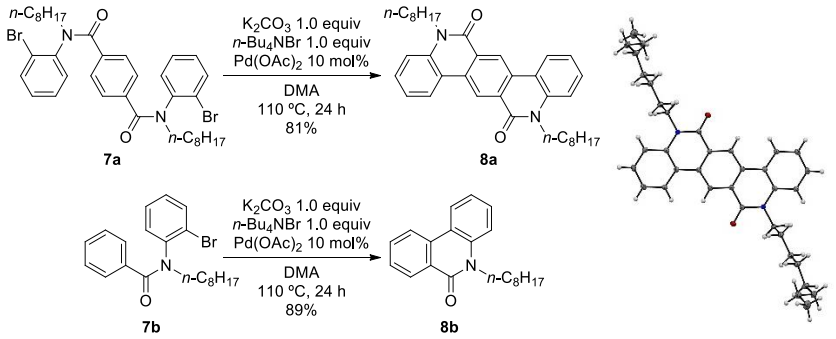
Substrate	Conc.[a]	*n*-Bu_4NBr (equiv)	Ligand	Product	Yield (%)[b]
 **1a**	0.033	1.0	none	**2a**	59
1a	0.033	1.0	PPh_3	**2a**	94
 **1b**	0.033	1.0	None	**2b**	18
1b	0.033	1.0	PCy_3	**2b**	47

1b	0.033	1.0	PPh_3	**2b**	58
1b	0.033	1.0	L1[c]	**2b**	70
 **1c**	0.033	1.0	none	**2c**	5[d]
1c	0.067	1.0	none	**2c**	11
1c	0.067	1.0	PPh_3	**2c**	24
1c	0.067	1.0	L1	**2c**	33
1c	0.067	1.0	PCy_3	**2c**	42
1c	0.067	1.0[e]	PCy_3	**2c**	77
 **3**	0.032	2.0	none	**4**	87
 **5a**	0.032	1.0	none	**6a**	51
 **5b**	0.032	2.0	none	**6b**	85[f]

[a]Substrate/DMA (mol/L); [b]yield determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as an internal standard; [c]L1 = CyJohnPhos (see Table1, footnote e); [d]isolated yield; [e] *n*-Bu_4NBr / *t*-BuCOOH (1:1) was used as an additive; [f]the result referred from ref [21].

It was also found that the related reaction also proceeded in the use of a carbocyclic amide derivative. When the reaction was carried out with **7a** under similar conditions, the cyclization occurred to afford **8a** in 81% yield as shown in Scheme 2. The formation of **8a** was confirmed by the X-ray crystallographic analysis (CCDC 2227450). The related mono-functional analog **7b** also underwent smooth cyclization

to afford **8b** in 89% yield under similar conditions, in which the result contrasted with the case of heterocyclic amide **1c** and **3** vs. **5a** and **5b**.



Scheme 2. Palladium-catalyzed intramolecular direct arylation for synthesizing **8a** and **8b** and the X-ray crystallographic structure of **8a**

Conclusion

We have shown facile synthesis of fused nitrogen-containing heterocycles and extended the scope of the palladium catalyzed C–H arylation to pyridine derivatives. The cyclization reaction proceeded in a moderate to excellent yield when an appropriate phosphine ligand was employed. The reaction is useful for the synthesis of functional materials, and bioactive molecules in a facile manner.

Experimental

Typical experimental procedure for C–H arylation of pyridine derivatives representative as 5-octyldibenzo[*b*,*f*][1,7]naphthyridin-6(5*H*)-one (**2a**)

To a screw-capped test tube equipped with a magnetic stirring bar were added amide **1a** (44.1 mg, 0.100 mmol), potassium carbonate (42.0 mg, 0.304 mmol), tetrabutylammonium bromide (31.7 mg, 0.098 mmol), $Pd(OAc)_2$ (2.2 mg, 10 mol%) and triphenylphosphine (2.8 mg, 10 mol%). The mixture was dissolved in 3.1 mL of DMA and stirring was continued at 110 ºC for 24 h. Water (3 mL) was added after cooling to

room temperature. The product was extracted with dichloromethane (2 mL) three times. The combined organic extracts were repeatedly washed with water (20 mL) and brine (20 mL). The organic lyaer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/MeOAc = 1:1) to provide 31.0 mg of **2a** as a colorless solid (87%). Mp 85.1–86.6 ºC; ^{1}H NMR ($CDCl_3$): δ 8.98 (s, 1H), 8.43 (d, *J* = 8.4 Hz, 1H), 8.31 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.76 (ddd, *J* = 8.0, 7.6, 1.2 Hz, 1H), 7.62 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.54 (ddd, *J* = 8.4, 8.0, 1.2 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.30 (dd, *J* = 8.0, 7.6 Hz , 1H), 4.40 (dd, *J* = 8.0, 7.6 Hz, 2H), 1.76–1.88 (m, 2H), 1.44–1.56 (m, 2H), 1.18–1.42 (m, 8H), 0.86 (t, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 160.1, 148.4, 142.0, 136.7, 131.1, 130.5, 130.2, 130.1, 129.1, 128.7, 127.7, 126.3, 123.8, 122.7, 118.3, 115.4, 43.3, 31.9, 29.5, 29.3, 27.3, 27.1, 22.7, 14.2; IR (ATR): 2959, 2929, 2856, 1661, 751 cm^{-1}; HRMS (DART+) m/z calcd. for $C_{24}H_{27}N_2O$, 359.2123 $[M+H]^+$; found, 359.2134.

Supporting Information

Accession code CCDC 2227450 contains the supplementary crystallographic data for **8a**. This data can be obtained free of charge via https://www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Additional experimental details and copies of ^{1}H and ^{13}C{^{1}H} NMR spectra

File Name: Supporting Information

File Format: PDF

Acknowledgements

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References

(1) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH Verlag GmbH: Weinheim, Germany, 1998. doi:10.1002/9783527612222

(2) *Metal-Catalyzed Cross-Coupling Reactions and More*; de Meijere, A.; Bräse, S.; Oestreich, M., Eds.; Wiley: Weinheim, Germany, 2014. doi:10.1002/9783527655588

(3) Bohra, H.; Wang, M. *J. Mater. Chem. A* **2017**, *5*, 11550–11571. doi:10.1039/C7TA00617A

(4) Albano, G.; Punzi, A.; Capozzi, M. A. M.; Farinola, G. M. *Green Chem.* **2022**, *24*, 1809–1894. doi:10.1039/D1GC03168F

(5) Hartwig, J. F. *Pure Appl. Chem.* **1999**, *71*, 1417–1423. doi:10.1351/pac199971081417

(6) Guo, Z.; Yan, C.; Zhu, W. *Angew. Chem. Int. Ed.* **2020**, *59*, 9812–9825. doi:10.1002/anie.201913249

(7) Yu, C. P.; Yamamoto, A.; Kumagai, S.; Takeya, J.; Okamoto, T. *Angew. Chem. Int. Ed.* **2023**, *62*, e202206417. doi:10.1002/anie.202206417

(8) Michael, J. P. *Nat. Prod. Rep.* **2002**, *19*, 742–760. doi:10.1039/b104971m

(9) Shang, X.; Morris - Natschke, S. L.; Liu, Y.; Guo, X.; Xu, X.; Goto, M.; Li, J.; Yang, G.; Lee, K. *Med. Res. Rev.* **2018**, *38*, 775–828. doi:10.1002/med.21466

(10) Yadav, T. T.; Murahari, M.; Peters, G. J.; YC, M. *Eur. J. Med. Chem.* **2022**, *239*, 114527. doi:10.1016/j.ejmech.2022.114527

(11) Shimada, A.; Yaita, T.; Narita, H.; Tachimori, S.; Kimura, T.; Okuno, K.; Nakano, Y. *Solvent Extr. Res. Dev., Jpn.* **2004**, *11*, 1–10.

(12) Xiao, C. L.; Wang, C. Z.; Yuan, L. Y.; Li, B.; He, H.; Wang, S.; Zhao, Y. L.; Chai, Z. F.; Shi, W. Q. *Inorg. Chem.* **2014**, *53*, 1712–1720. doi:10.1021/ic402784c

(13) Alyapyshev, M.; Ashina, J.; Dar'In, D.; Kenf, E.; Kirsanov, D.; Tkachenko, L.; Legin, A.; Starova, G.; Babain, V. *RSC Adv.* **2016**, *6*, 68642–68652. doi:10.1039/c6ra08946a

(14) Nakase, M.; Kobayashi, T.; Shiwaku, H.; Suzuki, S.; Grimes, T. S.; Mincher, B. J.; Yaita, T. *Solvent Extr. Ion Exch.* **2018**, *36*, 633–646. doi:10.1080/07366299.2018.1532137

(15) Healy, M. R.; Ivanov, A. S.; Karslyan, Y.; Bryantsev, V. S.; Moyer, B. A.; Jansone-Popova, S. *Chem. – Eur. J.* **2019**, *25*, 6326–6331. doi:10.1002/chem.201806443

(16) Simonnet, M.; Suzuki, S.; Miyazaki, Y.; Kobayashi, T.; Yokoyama, K.; Yaita, T. *Solvent Extr. Ion Exch.* **2020**, *38*, 430–440. doi:10.1080/07366299.2020.1744806

(17) Simonnet, M.; Kobayashi, T.; Shimojo, K.; Yokoyama, K.; Yaita, T. *Inorg. Chem.* **2021**, *60*, 13409–13418. doi:10.1021/acs.inorgchem.1c01729

(18) Wang, S.; Yang, X.; Xu, L.; Miao, Y.; Yang, X.; Xiao, C. *Ind. Eng. Chem. Res.* **2023**, *62*, 15613–15624. doi:10.1021/acs.iecr.3c02101

(19) Wang, S.; Yang, X.; Xu, L.; Xiao, C. *Ind. Eng. Chem. Res.* **2024**, *63*, 10773–10781. doi:10.1021/acs.iecr.4c01205

(20) Pramanik, S.; Li, B.; Driscoll, D. M.; Johnson, K. R.; Evans, B. R.; Damron, J. T.; Ivanov, A. S.; Jiang, D.; Einkauf, J.; Popovs, I.; Jansone-Popova, S. *J. Am. Chem. Soc.* **2024**, *146*, 25669–25679. doi:10.1021/jacs.4c07332

(21) Asano, T.; Nakanishi, Y.; Sugita, S.; Okano, K.; Narita, H.; Kobayashi, T.; Yaita, T.; Mori, A. *ChemRxiv* **2024**. This content is a preprint and has not been peer-reviewed. doi:10.26434/CHEMRXIV-2024-8LPMZ

(22) García-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066–1067. doi:10.1021/ja056165v

(23) Takagi, K.; Maeda, A.; Tsunekawa, R. *Results in Chemistry* **2022**, *4*, 100432. doi:10.1016/j.rechem.2022.100432

(24) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186–9187. doi:10.1021/ja049017y

(25) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581–590. doi:10.1021/ja055819x

(26) Liégault, B.; Petrov, I.; Gorelsky, S. I.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 1047–1060. doi:10.1021/jo902515z

(27) Majumdar, K. C.; De, N.; Chakravorty, S. *Synth. Commun.* **2010**, *41*, 121–130. doi:10.1080/00397910903531870

(28) Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 6338–6361. doi:10.1002/anie.200800497