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Arai, Nobumichi
Takahashi, Masabumi
Mitani, Makoto
Mori, Atsunori

Palladium-catalyzed intramolecular CH arylation of five-membered *N*-heterocycles[#]

Nobumichi Arai,[a] Masabumi Takahashi,[a] Makoto Mitani,[a] Atsunori Mori*[ab]

[a] Chemical Resources Laboratory, Tokyo Institute of Technology, R1-4, 4259 Nagatsuta, Yokohama 226-8503, Japan

[b] Department of Chemical Science and Engineering, Kobe University, 1-1 Rokkodai, Nada, Kobe 657-8501, Japan

Fax +81788036181; E-mail: amori@kobe-u.ac.jp

Received @@@.

Abstract: Intramolecular CH arylation of imidazole derivatives is carried out in the presence of a palladium catalyst to form fused heteroaromatic compounds. The reaction of imidazole with 2-iodobenzyl bromide with NaH gives the cyclization precursor **1a** in an excellent yield. Palladium-catalyzed reaction of **1a** undergoes intramolecular CH arylation at 100 °C to form 5H-imidazo[5,1-a]isoindole (**2a**) in 78% yield.

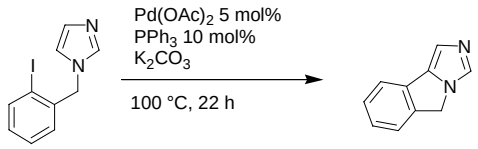
Key words: intramolecular C-H arylation, palladium catalyst, imidazole derivatives, one-pot reaction

Synthesis of fused heteroaromatic compounds is of considerable interest in organic synthesis since a wide variety of such molecules show biological activities as pharmaceutical and agrochemical compounds.[1] Intramolecular arylation of the CH bond of a heteroaromatic compound is the method of a practical choice. Although several studies with a palladium-catalyzed strategy have been performed,[2] intramolecular version of *N*-(2-halobenzyl)-heteroaromatics has not been studied so far. Since introduction of the cyclization precursor can easily be performed by the *N*-alkylation of the unsubstituted heterocycle, the reaction can be a facile method to constitute the fused ring system. Although the intermolecular CH arylation reported by Miura has shown to proceed in good to excellent yields, the reaction sometimes cause difficulties in the selectivity of 5-arylation and 2,5-diarylation.[3] Thereby, the intramolecular version might be a solution for such selectivity problem. On the other hand, we have been studying a transition metal-catalyzed CH arylation of heteroaromatic compounds such as thiazoles and thiophenes, which is shown to proceed under mild conditions when a certain additive is employed.[4] By contrast, the related CH arylation reaction of heterocycles bearing nitrogen atoms, as represented by imidazoles, pyrroles, and pyrazoles, occurs under harsh conditions.[5] We therefore envisaged that the reaction takes place at a lower temperature when the reaction is applied to the intramolecular manner. Our effort on the design of the cyclization precursor and the intramolecular palladium-catalyzed CH arylation is described herein.

Synthesis of the cyclization precursor **1a** was carried out by the reaction of imidazole with 2-iodobenzyl bromide. Treatment of imidazole with sodium hydride followed by addition of 2-iodobenzyl bromide afforded **1a** in 88% yield. The related aryl bromide **1a'** was also prepared in a similar manner.

[#]Dedicated to Professor R. F. Heck and his contributions to chemistry.

The intramolecular CH arylation of **1a** was summarized in Table 1. When the reaction was carried out with **1a** in the presence of 5 mol% of $Pd(OAc)_2$-2(PPh_3) and K_2CO_3 (2 equiv) in DMSO at 100 °C for 22 h, 5H-imidazo[5,1-a]isoindole (**2a**) that is the intramolecular CH arylation product at the 5-position of imidazole was obtained in 78% yield. The use of $PdCl_2(PPh_3)_2$ was also found to be similarly effective. Among several aprotic polar solvents examined, DMSO resulted to give the highest yield, while other solvents such as DMF, DMAc (*N*,*N*-dimethylacetamide), NMP (*N*-methylpyrrolidone) were found to be slightly inferior. The effect of additive was also examined and potassium carbonate was found to be superior. The use of cesium carbonate, which was shown to be similarly effective to K_2CO_3 by Miura in the intermolecular coupling of imidazole, resulted in lower yield (38%).[3] On the other hand, the reaction in the presence of silver(I) oxide and silver(I) fluoride as an activator did not afford the cyclization product **2a** at all. Although the reaction of **1a** with a catalytic or stoichiometric amount of CuI was attempted, the reaction at the 2-position of the imidazole was found to be unsuccessful. When a catalytic amount of CuI was employed for the reaction, the product reacted at the 5-position of **1a** was obtained in a lower yield. However, **2a** was not obtained at all along with a mixture of unidentified products in the reaction with 200 mol% of CuI. Although the reason for the unsuccessful reaction with CuI for the intramolecular cyclization has not been clear yet, the difficulty would be due to the strained structure of the product that is reacted at the 2-position of the imidazole ring. Several examples of the intramolecular cyclization by generation of radical has shown to produce the similar fused heteroaromatic compounds, however, the palladium-catalyzed reaction seems to proceed with higher efficiency.[6]



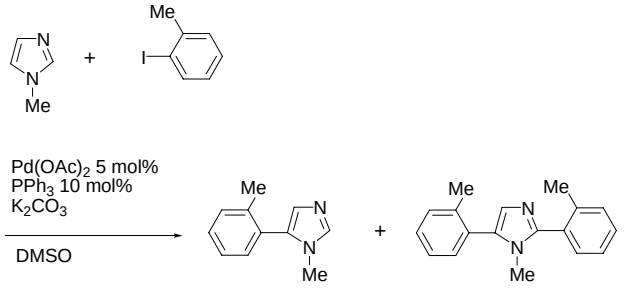
1a **2a**

Table 1. Intramolecular CH arylation of **1a** in the presence of a palladium catalyst.[a]

catalyst (mol %)	solvent	additive	yield/%
$Pd(OAc)_2$-2PPh_3 (5)	DMSO	K_2CO_3	78
	DMF	K_2CO_3	41
	DMAc	K_2CO_3	47
	NMP	K_2CO_3	58
	DMSO	Cs_2CO_3	38
	DMSO	Ag_2O[b]	0
	DMSO	AgF	0
$PdCl_2(PPh_3)_2$ (5)	DMSO	K_2CO_3	55
$Pd(OAc)_2$-2PPh_3 (5) CuI (2)	DMSO	K_2CO_3	42
$Pd(OAc)_2$-2PPh_3 (5) CuI (10)	DMSO	K_2CO_3	18
$Pd(OAc)_2$-2PPh_3 (5) CuI (200)	DMSO	K_2CO_3	0[c]

[a] Unless noted, the reaction was carried out with **1a** (0.5 mmol), additive (1.0 mmol), and 3 mL of solvent at 100 °C for 22 h. [b] The amount of Ag_2O was 0.5 mmol. [c] No cyclization at the 2-position was observed to afford a mixture of unidentified products.

The intramolecular CH arylation reaction appeared to proceed under milder conditions than the intermolecular reaction. Indeed, the attempted reaction of N-methylimidazole with 2-iodotoluene resulted in no reaction under similar conditions (100 °C, 24 h). The reaction was found to take place at the elevated temperature (140 °C), however, the reaction was hardly controlled to afford the mixture of 5-arylated product **3** and 2,5-diarylated product **4** in 50% and 21% yields, respectively.[7] The results suggest that the intramolecular CH arylation reaction shows regiochemical control as well as enhanced reactivity.

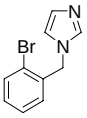
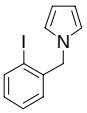
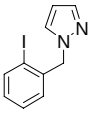


3 **4**

100 °C:	0%	0%
140 °C:	50%	21%

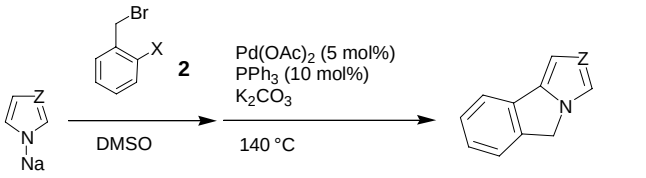
Table 2 summarizes the intramolecular reactions of imidazole derivatives and other five-membered heteroaromatic compounds. The reaction with bromide **1a'** was also found to take place. Although the reaction at 100 °C resulted in giving lower yield, the yield was improved to 77% at 140 °C. The reaction with pyrrole derivative **1b**, whose preparation was carried out with 2-iodobenzyl bromide and pyrrole in 63% yield, also proceeded smoothly to give 5H-pyrrolo[2,1-a]isoindole (**2b**) in 82% yield. Although the related intramolecular reaction with pyrazole derivative **1c** was examined, the desired cyclized product was not obtained.

Table 2. Intramolecular CH arylation in the presence of $PdCl_2(PPh_3)_2$.[a]

1	temp/°C	time/h	yield/%
 **1a'**	100	24	61
	140	24	77
 **1b**	100	27	82
 **1c**	140	24	0

[a] The reaction was carried out with **1** (0.5 mmol), $PdCl_2(PPh_3)_2$ (5 mol %), potassium carbonate (1.0 mmol) in 3 mL of DMSO under an argon atmosphere.

It was also found that construction of fused heteroaromatic ring is possible by the one-pot reaction of the sodium salt of imidazole with 2-halobenzyl bromide. Treatment of the sodium salt of imidazole, which was prepared by the reaction of imidazole with sodium hydride in situ, with 2-iodobenzyl bromide followed by the addition of the palladium catalyst and potassium carbonate afforded **2a** in 55% yield after stirring for 48 h at 140 °C. The reaction with 2-bromobenzyl bromide also afforded **2a** although the yield was slightly lower (44%). In addition, the reaction with pyrrole to form **2b** proceeded in 48% yield in a similar one-pot protocol.



2a (X=I, Z=N): 55 %
2a (X=Br, Z=N): 44 %
2b (X=I, Z=CH): 48%

In summary, palladium-catalyzed CH arylation of imidazole derivative was performed in the intramolecular version, which was a facile preparation protocol for the fused heteroaromatic compounds. The reaction was found to proceed under mild conditions compared with the corresponding intermolecular CH arylation. The method would be applicable for several other ring systems and heteroatom species.

Experimental.

1-(2-Iodobenzyl)-1H-imidazole (**1a**)**:** To a 25 mL of two-necked flask equipped with a magnetic stirring bar were added sodium hydride (48.0 mg, 2 mmol) and 3 mL of THF under an argon atmosphere. Imidazole (68.1 mg, 1 mmol) was then added. After the evolution of hydrogen stopped, 2-iodobenzyl bromide (296.9 mg, 1 mmol) was added and stirring was continued at room temperature for 1 h. The mixture was poured into a mixture of 20 mL of water and 20 mL of diethyl ether and the two phases were separated. The aqueous layer was extracted with diethyl ether twice and the combined organic layer was dried over anhydrous sodium sulfate. Concentration of the solvent under reduced pressure left a crude oil, which was purified by column chromatography on silica gel using hexanes: ethyl acetate = 1:1 as an eluent to afford 236.7 mg of **1a** as a colorless oil (88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.10 (2H, s), 6.81(1H, d, *J* = 7.5 Hz), 6.88 (1H, s), 6.97 (1H, dd, *J* = 7.8, 7.8 Hz), 7.06 (1H, s), 7.26 (1H, dd, *J* = 7.5 Hz), 7.54 (1H, s), 7.82 (1H, d, *J* = 7.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.6, 98.3, 119.6, 128.8, 129.1, 129.9, 130.2, 137.9, 138.8, 140.0. IR (KBr) 3109, 1508, 1238, 1074, 1014, 868, 748, 735, 663 cm^{-1}. HRMS found: m/z 283.9826. Calcd for 283.9810.

5H-Imidazo[5,1-a]isoindole (**2a**)**:** To a 25 mL of Schlenk tube equipped with a magnetic stirring bar was added K_2CO_3 (135.2 mg, 1 mmol). The Schlenk tube was heated at 140 °C for 2 h under vacuum and the atmosphere was replaced with argon. Then, **1a** (142.1 mg, 0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), triphenylphosphine (13.1 mg, 0.05 mmol), and 3 mL of DMSO were added and the resulting mixture was heated at 100 °C for 22 h. After cooling to room temperature the mixture was diluted with 20 mL of ethyl acetate and passed through a Celite pad. The cake was washed with 10 mL of ethyl acetate. To the filtrate was added 20 mL of water. The mixture was vigorously shaken and the two phases were separated. The organic layer was washed twice with water and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure left a crude solid, which was purified by chromatography on silica gel using hexane : ethyl acetate = 1:3 as an eluent to afford 61.1 mg of **2a**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.00 (2H, s), 7.18 (1H, s), 7.24 (1H, dd, *J* = 7.5, 7.5), 7.37 (1H, dd, *J* = 8.1, 8.1), 7.39 (1H, d, *J* = 7.5 Hz), 7.55 (1H, d, *J* = 7.2 Hz), 7.72 (1H, s,). ^{13}C NMR ($CDCl_3$) δ 48.8, 118.6, 120.3, 123.9, 126.6, 128.6, 130.7, 132.5, 138.9, 140.6. IR (KBr) 3103, 1618, 1485, 1454, 1437, 1084, 929, 758, 652 cm^{-1}. HRMS Found: m/z 156.0676. Calcd for 156.0687.

One-pot synthesis of 2a with 1a and imidazole sodium salt: To a 25 mL of Schlenk tube equipped with a magnetic stirring bar were added NaH (12.0 mg, 0.5 mmol), imidazole (34.0 mg, 0.5 mmol) and 3 mL of DMSO. The mixture was stirred for 2 h at room temperature to form the sodium salt. Then, 2-iodobenzyl bromide (148.5 mg, 0.5 mmol) was added and stirring was continued for further 3 h at room temperature. Potassium carbonate (138.2 mg, 1 mmol), which was dried under vacuum at 140 °C for 2 h, $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), and triphenylphosphine (13.1 mg, 0.05 mmol) were added to the mixture and stirring at 140 °C was continued for 27 h. After the reaction is complete, isolation and purification procedures were carried out in a similar manner to the above mentioned palladium-catalyzed reactions.

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(7) The ratio of **3** and **4** was consistent with the Miura's results. (See ref 3a)

Graphical abstract

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intramolecular C-H arylation, palladium catalyst, imidazole derivatives, one-pot reaction