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PALLADIUM-ASSISTED BIARYL COUPLING REACTION OF 1-(2- IODOBENZOYL)-1,2,3,4-TETRAHYDROQUINOLINE

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Abstract – The biaryl coupling reaction of 1-(2-iodobenzoyl)-1,2,3,4-tetrahydroquinoline using Pd reagent was examined. The reaction proceeded smoothly to produce 5,6-dihydro-4*H*,8*H*-pyrido[3,2,1-*de*]phenanthridin-8-one in excellent yield.

In a preliminary study of the synthesis of pyrrolophenanthridine alkaloids, the intramolecular biaryl coupling reaction of 1-(2-iodobenzoyl)-2,3-dihydroindole (**1**) using Pd(OAc)₂ and K₂CO₃ in DMF was examined, and the reaction produced the desired dihydropyrrolophenanthridone (**2**) in only 8% yield.¹ (The yield was improved to 20% after re-examination. See run 11 in Table 1.) However, Cai *et al.* reported that the reaction of 1-[(6-bromo-1,3-benzodioxol-5-yl)carbonyl]-2,3-dihydroindole (**3**) using Pd(OAc)₂ and K₂CO₃ in DMA in the absence of phosphine ligand afforded pyrrolophenanthridone (**4**) in 55% yield.² Thus, we examined the reaction of 1-[(6-iodo-1,3-benzodioxol-5-yl)carbonyl]-2,3-dihydroindole (**5**), which should be more reactive than **3**, under their reaction conditions, but we could not obtain **4**, even in the presence of a phosphine ligand.³ Miki *et al.* reported that the reaction of 1-(2-bromo-4,5-dimethoxybenzoyl)indole-2,3-dicarboxylate (**6**) with Pd(PPh₃)₄ gave no coupling product.⁴ These results seem to be in conflict. Therefore, we re-examined the biaryl coupling reaction of **1**. Subsequently, we investigated the reaction of 1-(2-iodobenzoyl)tetrahydroquinoline (**7**) using Pd reagent in order to examine the effect of ring size, *i.e.*, dihydroindole has a five-membered ring, and tetrahydroquinoline has a six-membered ring. When it works well, the method will provide a new and concise synthesis of 5,6-dihydro-4*H*,8*H*-pyrido[3,2,1-*de*]phenanthridin-8-one (**8**),⁵ which is an isomer of aporphine alkaloid, using the Pd-assisted biaryl coupling reaction.^{6,7}

First, the coupling reaction of **7** was examined. The starting materials (**7**) for the coupling reaction were

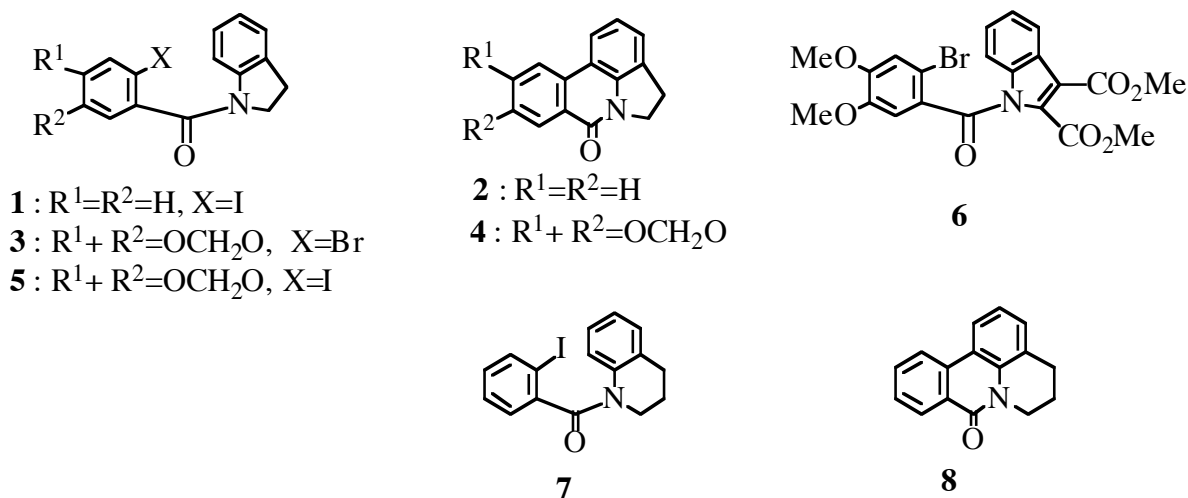


Table 1. Results of coupling reaction of 1-(2-iodobenzoyl)tetrahydroquinoline (**7**) and 1-(2-iodobenzoyl)dihydroindole (**1**).^{a)}

starting material	run	Pd reagent (10 mol%)	phosphine (P/Pd) ^{b)}	base	time (h)	yield (%)
7	1	Pd(OAc) ₂	P(<i>o</i> -tol) ₃ (2)	K ₂ CO ₃	1.0	98
	2	Pd(OAc) ₂	PBu ₃ (2)	K ₂ CO ₃	2.0	91
	3	PdCl ₂ (PPh ₃) ₂	-	AcONa	0.5	90
	4	Pd(OAc) ₂	PCy ₃ (2)	K ₂ CO ₃	0.5	90
	5	Pd(OAc) ₂	-	K ₂ CO ₃	3.0	88
	6	Pd(OAc) ₂	PPh ₃ (2)	K ₂ CO ₃	2.0	88
	7 ^{c)}	Pd(OAc) ₂	<i>n</i> -Bu ₃ P (1), DPPP (1)	K ₂ CO ₃	2.0	89
1	8	Pd(OAc) ₂	P(<i>o</i> -tol) ₃ (2)	K ₂ CO ₃	4.0	-
	9	Pd(OAc) ₂	PBu ₃ (2)	K ₂ CO ₃	4.0	22
	10	PdCl ₂ (PPh ₃) ₂	-	AcONa	4.0	-
	11 ^{d)}	Pd(OAc) ₂	-	K ₂ CO ₃	4.0	20
	12 ^{e)}	Pd(OAc) ₂	-	K ₂ CO ₃	4.0	20 ^{f)}
	13 ^{e)}	Pd(OAc) ₂	PPh ₃ (2)	K ₂ CO ₃	4.0	-
	14 ^{c, e)}	Pd(OAc) ₂	<i>n</i> -Bu ₃ P (1), DPPP (1)	K ₂ CO ₃	4.0	-

a) The reaction was carried out using Pd(OAc)₂ (10 mol%), base (200 mol%) in DMF under reflux. b) Molar ratio between phosphine and Pd. c) See reference 6e). d) Sc(OTf)₃ (100 mol%) was added. e) See reference 1. f) Yield was improved,

prepared from tetrahydroquinoline and 2-iodobenzoyl chloride in 80% yield. The results of the coupling reaction of **7** are summarized in Table 1. In general, the reaction proceeded smoothly to produce pyrido[3,2,1-*de*]phenanthridin-8-one (**8**)⁵ in excellent yield. In addition, the reactions of **1** under several reaction conditions, including previously reported conditions,¹ were (re)examined. However, the cyclized product (**2**) was obtained in at most 22% yield using Pd(OAc)₂, Bu₃P, and K₂CO₃ (see run 9 in Table 1) even using the reaction conditions under which the cyclization reaction of **7** worked well. A similar difference in the behaviors of benzoyltetrahydroquinoline (**7**) and benzoyldihydroindole (**1**) was reported for the Pshorr reactions of 1-(2-aminobenzoyl)tetrahydroquinoline and 1-(2-aminobenzoyl)dihydroindole, in which authors suggested that the difference could be attributable to the favorable conformation of tetrahydroquinoline to the cyclization and/or the less strained structure of **8** than **2**.^{5a} The results using

palladium reagents were similar to those of the Pshorr reactions.

In conclusion, the Pd-assisted biaryl coupling reaction of 1-(2-halobenzoyl)tetrahydroquinoline is a concise and versatile procedure for synthesizing pyridophenanthridone derivatives.

EXPERIMENTAL

Melting points were measured on a micro-melting point hot-stage apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded on a JASCO FT/IR 350 spectrophotometer and ^1H -NMR spectra in an indicated solvent on Varian VXR-300 (300 MHz) spectrometers, unless otherwise stated. NMR spectral data are reported in parts per million downfield from tetramethylsilane as an internal standard (δ 0.0), and the coupling constants are given in Hertz. Column chromatography was carried out on a Merck silica gel (230-400 mesh). All the extracts were washed with brine, dried over anhydrous MgSO_4 , and filtered; the filtrate was concentrated to dryness under reduced pressure. $\text{Pd}(\text{OAc})_2$ was treated with boiling benzene, and the mixture was filtered while hot. The hot filtrate was then concentrated to dryness to give purified $\text{Pd}(\text{OAc})_2$.

1-(2-Iodobenzoyl)-1,2,3,4-tetrahydroquinoline (7)

A solution of 2-iodobenzoic acid (9.92 g, 40 mmol) in a few drops of dry DMF and thionyl chloride (4.4 mL, 60 mmol) was refluxed for 30 min and concentrated to dryness under reduced pressure. To this residue was added a solution of tetrahydroquinoline (6.39 g, 48 mmol) in dry CH_2Cl_2 (60 mL) and dry NEt_3 (7.3 mL), and the mixture was stirred for 40 min at rt. The reaction mixture was poured into 10% HCl and extracted with CHCl_3 . The organic layer was washed with 1 N HCl, aqueous sat. NaHCO_3 solution, and brine. The residue was recrystallized from ether to give **7** (11.55 g, 80%) as colorless plates, mp 137-139°C. IR (KBr) cm^{-1} : 1625. ^1H -NMR (300 MHz, $\text{DMSO}-d_6$ at 80°C) δ : 1.99 (2H, tt $J=6.6$, 6.6 Hz), 2.83 (2H, t, $J=6.6$ Hz), 3.64 (2H, br s), 6.99 (2H, m), 7.14 (3H, m), 7.29 (1H, br d, $J=7.2$ Hz), 7.41 (1H, dd, $J=7.5$, 7.5 Hz), 7.82 (1H, br d, $J=8.1$ Hz). *Anal.* Calcd for $\text{C}_{16}\text{H}_{14}\text{NOI}$: C, 52.91; H, 3.89; N, 3.86. Found: C, 52.83; H, 3.84; N, 3.85.

General Procedure for the Coupling Reaction of 1-(2-Iodobenzoyl)-1,2,3,4-tetrahydroquinoline (7) (runs 1 ~ 7 in Table 1)

1-(2-Iodobenzoyl)tetrahydroquinoline (**7**) (105 mg, 0.3 mmol) was reacted with $\text{Pd}(\text{OAc})_2$, a phosphine ligand, and 200 mol% of base in dry DMF (8 mL) under reflux for the time indicated in Table 1. Then, the reaction mixture was diluted with AcOEt, and the precipitates were removed by filtration. The filtrate was washed with brine. The residue dissolved in CHCl_3 was subjected to column chromatography on silica gel. Elution with hexane-AcOEt (4:1) gave 5,6-dihydro-4*H*,8*H*-pyrido[3,2,1-*de*]phenanthridin-8-one (**8**) as colorless pillars (ether), mp 94-96°C (lit.,^{5a} 94-95°C, lit.,^{5b} 180-182°C). IR (KBr) cm^{-1} : 1646. ^1H -NMR (300 MHz, CDCl_3) δ : 2.13 (2H, tt $J=6.1$, 6.1 Hz), 3.02 (2H, t, $J=6.1$ Hz), 4.32 (2H, t, $J=6.1$ Hz),

7.21 (1H, dd, $J=7.5$, 7.5 Hz), 7.30 (1H, dd, $J=0.6$, 7.5 Hz), 7.58 (1H, ddd, $J=1.0$, 7.5, 7.5 Hz), 7.75 (1H, ddd, $J=1.5$, 7.5, 7.8 Hz), 8.13 (1H, dd, $J=1.0$, 7.8 Hz), 8.27 (1H, dd, $J=0.6$, 7.5 Hz), 8.54 (1H, dd, $J=1.5$, 7.5 Hz). *Anal.* Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.89; H, 5.66; N, 5.93.

The Coupling Reaction of 1-benzoyl-7-iodo-2,3-dihydroindole (1) using Pd reagent (runs 8 ~ 11 in Table 1)

The reactions and work-up were carried out according to the reported procedure.¹ Only the yields of **2** are given in the Table.

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