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CONCISE SYNTHESIS OF 11*H*-INDOLIZINO[1,2-*b*]QUINOLIN-9-ONE BY AN ARYL-ARYL COUPLING REACTION USING Pd REAGENT

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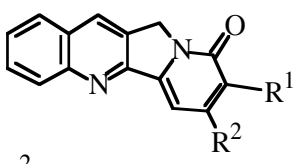
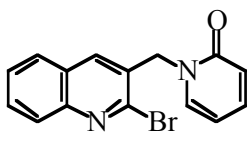
Abstract – The biaryl coupling reaction of 1-[(2-bromoquinoline-3-yl)methyl]-2(1*H*)-pyridinone using a catalytic amount of palladium acetate, tricyclohexylphosphine, and potassium acetate in DMF proceeded smoothly to give 11*H*-indolizino[1,2-*b*]quinolin-9-one in excellent yield.

Aryl-aryl coupling reactions using a palladium reagent have been used to synthesize many condensed aromatic compounds.[1] Recently, we reported the synthesis of condensed aromatic alkaloids[2] using intramolecular biaryl coupling reactions with palladium reagents and the synthesis of naphthobenzazepines by regioselective C-H bond activation using the intramolecular coordination of the amine to Pd.[3]

Now, we envision establishing the biaryl coupling reaction conditions for synthesizing 11*H*-indolizino[1,2-*b*]quinoline (**1**) from 1-[(2-bromoquinoline-3-yl)methyl]-2(1*H*)-pyridinone (**2**) using Pd reagents as a preliminary study of the synthesis of mappicine ketone (**3**), although Comins *et al.* already reported the synthesis of **3** in 57% yield using $Pd(OAc)_2$, tetrabutylammonium bromide, and KOAc in CH_3CN.[4]



1 : R^1=R^2=H



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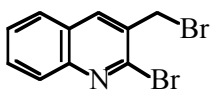

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3 : R^1=CH_3, R^2=COC_2H_5 (mappicine ketone)

Fig. 1

The starting material (**2**) for the coupling reaction was synthesized as follows. *N*-Alkylation of 2-hydroxypyridine with 2-bromo-3-bromomethylquinoline (**4**)[5] in the presence of potassium *tert*-butoxide gave **2** in 84% yield. The biaryl coupling reaction of **2** to 11*H*-indolizino[1,2-*b*]quinoline (**1**) using the Pd reagent in DMF under reflux was examined and the results are summarized in Table 1. The biaryl coupling reactions using our novel method[2d] (run 5) and Jeffery's conditions[6] (run 9) were not fruitful. Reactions using $(o\text{-Tol})_3P$ as the ligand (runs 1 and 2) or cesium carbonate (run 7) as the base did not proceed. However, using tricyclohexylphosphine (Cy_3P) as the ligand and potassium acetate as the base, the coupling reaction proceeded smoothly to give **1**[7] in 96% yield (see run 4).

This procedure is now being applied to the synthesis of heteroaromatic compounds.

Table 1. Results of biaryl coupling reactions of 1-[(2-bromoquinoline-3-yl)methyl]-2(1*H*)-pyridinone (**2**) to 11*H*-indolizino[1,2-*b*]quinoline (**1**) in DMF under reflux

run	Pd (eq.)	ligand (L/Pd)	additive (eq.)	base (eq.)	time	yield (%)
1	$Pd(OAc)_2$ (0.1)	$(o\text{-Tol})_3P$(2)	---	K_2CO_3 (2.0)	20 min	---[a)]
2	$Pd_2(dba)_3$ (0.1)	$(o\text{-Tol})_3P$(2)	---	K_2CO_3 (2.0)	10 min	trace
3	$Pd(OAc)_2$ (0.1)	Cy_3P (2)	---	K_2CO_3 (2.0)	20 min	63
4	$Pd(OAc)_2$ (0.1)	Cy_3P (2)	---	KOAc (2.0)	20 min	96
5	$Pd(OAc)_2$ (1.0)	$n\text{-Bu}_3P$ (1)	---	K_2CO_3 (2.0)	20 min	45
		DPPP (1)	---			
6	$Pd(OAc)_2$ (0.1)	$n\text{-Bu}_3P$ (1)	---	K_2CO_3 (2.0)	10 min	54
		DPPP (1)	---			
7	$Pd(OAc)_2$ (0.1)	$n\text{-Bu}_3P$ (2)	---	Cs_2CO_3 (2.0)	70 min	---[a)]
8	$Pd(OAc)_2$ (0.1)	$n\text{-Bu}_3P$ (2)	---	K_2CO_3 (2.0)	10 min	73
9	$Pd(OAc)_2$ (0.1)	---	Bu_4NCl (1)	KOAc (5.0)	10 min	54

a) many spots on TLC

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 ^{1}H-NMR spectra in deuteriochloroform on a Varian VXR-200 (200 MHz) spectrometer. The NMR spectral data are reported in parts per million downfield from tetramethylsilane as an internal standard (0.0) and the coupling constants are given in Hertz. MS spectra were obtained on a VG-70SE spectrometer. Column chromatography was carried out on a Merck, Kieselgel 60, No. 9385. All the experiments were carried out in an argon atmosphere and the extract was washed with brine, dried over anhydrous K_2CO_3, and filtered; the filtrate was concentrated to dryness under reduced pressure. $Pd(OAc)_2$ was treated with boiling benzene and the mixture was filtered while hot. The hot filtrate was then concentrated to dryness to give purified $Pd(OAc)_2$.

1-[(2-Bromoquinoline-3-yl)methyl]-2-(1*H*)-pyridinone (2)

A mixture of 2-hydroxypyridine (236 mg, 2.48 mmol) and *t*-BuOK (333 mg, 2.98 mmol) in DME (15 mL) was stirred at rt for 1 h and then 2-bromo-3-bromomethylquinoline (**4**) (746 mg, 2.48 mmol) was added to the reaction mixture. After stirring for 1 h, the reaction mixture was diluted with aqueous 5% Na_2CO_3 solution to bring the solution to pH 10 and extracted with AcOEt. The extract was washed with brine. The residue was recrystallized from AcOEt to give **2** (782 mg, 84%) as colorless plates, mp 155-158°C. IR (KBr) cm^{-1}: 3030, 1660. ^{1}H-NMR (200 MHz, $CDCl_3$) □: 5.35 (2H, s, N-CH_2), 6.24 (1H, br t, *J*=6.7 Hz, C_5-H in pyridone ring), 6.66 (1H, br d, *J*=9.6 Hz, C_3-H in pyridone ring), 7.4-7.8 (5H, m, aromatic protons), 7.91 (1H, s, C_4-H in quinoline ring), 8.00 (1H, br d, *J*=8.2 Hz, C_8-H in quinoline ring). MS (FAB positive ion mode) *m/z*: 316 (M+1), 318 (M+3). *Anal.* Calcd for $C_{15}H_{11}N_2OBr$: C, 57.16; H, 3.52; N,8.89. Found: C, 57.60; H, 3.80; N, 8.87.

General procedure for the coupling reaction of 1-[(2-bromoquinoline-3-yl)methyl]-2(1*H*)-pyridinone (2) (runs 1~8 in Table 1)

The starting material (**2**) (0.3 mmol) was reacted with $Pd(OAc)_2$, a phosphine ligand, and a base in dry DMF (4 mL) using $Pd(OAc)_2$, the phosphine ligand in the ratios indicated in Table 1 and 2 mol equivalents of the base for the times indicated in the Table under reflux. Then, the reaction mixture was diluted with AcOEt and the precipitate was removed by filtration. The filtrate was adjusted to pH 10 with aqueous 5% Na_2CO_3 solution and extracted with AcOEt. The extract was washed with brine. The residue dissolved in $CHCl_3$ was subjected to column chromatography on silica gel. Elution with AcOEt gave **1** as pale yellow needles (from EtOH) mp 267-269°C (lit.,[7] 265°C).

Coupling reaction of 1-[(2-bromoquinoline-3-yl)methyl]-2(1*H*)-pyridinone (2) under phosphine-free conditions (run 9 in Table 1) [6]

The starting material (**2**) (0.3 mmol) was reacted with 0.1 equivalent of $Pd(OAc)_2$, 1 equivalent of *n*-Bu_4NCl, and 5.0 equivalents of KOAc in dry DMF (4 mL) for 10 min under reflux. Then, the reaction mixture was treated using the procedure mentioned above. The coupling product (**1**) was obtained in 54% yield.

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