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INTRAMOLECULAR Pd-CATALYZED BIARYL COUPLING REACTION OF *N*-ARYL-2-TRIFLYLOXYBENZAMIDES USING $Pd(OAc)_2$, 1,3-BIS[DIPHENYLPHOSPHINO]PROPANE, Bu_3P, AND DBU

Hiromi Nishioka, Yoshimi Shoujiguchi, Hitoshi Abe, Yasuo Takeuchi, and Takashi Harayama*

Faculty of Pharmaceutical Sciences, Okayama University, Tsushima-naka 1-1-1, Okayama 700-8530, Japan
E-mail: harayama@pharm.okayama-u.ac.jp

Abstract – Intramolecular Pd-catalyzed coupling reactions of *N*-aryl-2-triflyloxybenzamides were examined. The procedure using DBU as a base was effective for even in the reaction of oxygen-substituted benzamides

In our studies of the synthesis of fully aromatized benzo[*c*]phenanthridine alkaloids, we found that a novel palladium reagent prepared from $Pd(OAc)_2$, together with 1,3-bis(diphenylphosphino)propane (DPPP), Bu_3P, and *i*-Pr_2NEt, was very versatile for coupling reactions between aryl triflate and arenes.[1] However, a stoichiometric amount of the palladium reagent was usually required to obtain the coupling product in a satisfactorily high yield. Although we reported a catalytic reaction using $Pd(OAc)_2$ (0.2 eq.) and Bu_3P (0.6 eq.), the procedure was not useful for coupling reactions between aryl triflate and arenes with oxygen functional group(s).[2] Therefore, we re-investigated the catalytic ability of our novel method.[1] Here, we describe the reaction conditions for palladium-catalyzed intramolecular coupling reactions of *N*-aryl-2-triflyloxybenzamides.

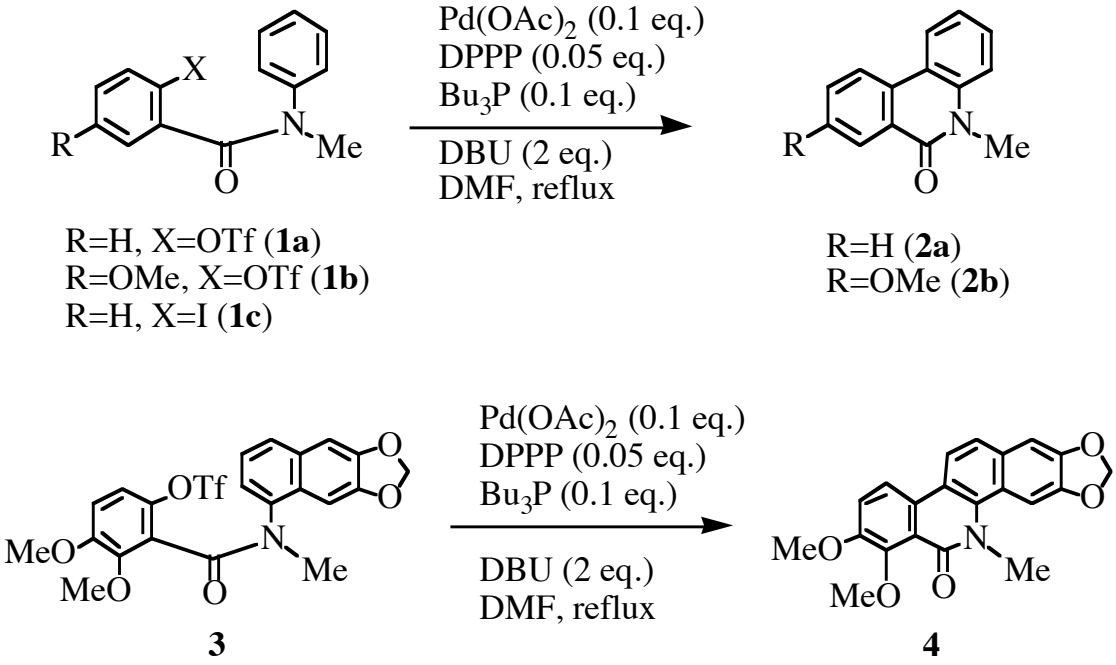
It has been reported that a palladium reagent catalyzed the intramolecular aryl triflate-arene coupling reaction using DBU as a base,[3a-c] while the addition of LiCl, which was thought necessary for Pd-catalyzed coupling reactions involving triflates, had a deleterious effect on the reaction of highly methoxylated substrates.[3d] Therefore, we examined the intramolecular coupling reaction of triflyloxybenzanilides (**1**) using $Pd(OAc)_2$ (0.1 eq.), DPPP (0.05 eq.), Bu_3P (0.1 eq.), and DBU (2 eq.) in DMF under reflux and in the absence of LiCl by considering the synthesis of oxychlerythrine (**4**) from the compound (**3**).[4]

The reaction of 2-(trifluoromethanesulfonyloxy)-*N*-methyl-*N*-phenylbenzamide (**1a**)[1b] under these reaction conditions proceeded smoothly to give *N*-methylphenanthridone (**2a**)[1b, 5] in 87% yield. This

This paper is dedicated to Dr. Pierre Potier on the Occasion of his 70th birthday.

procedure was applied to the coupling reaction of triflyloxy-phenylbenzamide (**1b**)[1b] possessing a methoxy group to produce **2b**[1b] in 93% yield. Furthermore, this procedure was proven effective for the cyclization reaction of **1c** possessing an iodo group to give **2a** in 84% yield. Then, the application of this method to the synthesis of chelerythrine from naphthylamide (**3**) was examined. The reaction of **3** for 45 min gave oxychelerythrine (**4**)[6] in 54% yield accompanied by the recovery of **3** in 30% yield.

In conclusion, this procedure using DBU as a base was effective for Pd-catalyzed coupling reactions of aryl triflate with arenes possessing oxygen substituent(s).



Scheme 1

EXPERIMENTAL

Melting points were measured on a micro-melting point hot-stage apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded in Nujol on a JASCO FT/IR 350 spectrophotometer and ^{1}H-NMR spectra were recorded in deuteriochloroform on a Varian VXR-200 (200-MHz) spectrometer unless otherwise stated. The NMR spectral data are reported in ppm downfield from tetramethylsilane as the internal standard (δ 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 silica gel (Wako gel C-200 or Merck, silica gel 60, No. 9385). All the experiments were carried out in an argon atmosphere and the extract was washed with brine, dried over anhydrous $MgSO_4$, then filtered, and the filtrate was evaporated to dryness under reduced pressure, unless otherwise noted. $Pd(OAc)_2$ was treated with boiling benzene and the mixture was filtered while hot. The hot filtrate was then concentrated to dryness to give purified $Pd(OAc)_2$.

General Procedure for the Coupling Reaction of *N*-Phenylbenzamides (1)

To a solution of **1** (0.3 mmol) in dry DMF (5 mL) were successively added Pd $(OAc)_2$ (6.5 mg, 0.03 mmol), DPPP (13.2 mg, 0.03 mmol), Bu_3P (7.2 μg, 0.03 mmol), and DBU (90 μg, 0.6 mmol). The mixture was refluxed for 30 min and the reaction mixture was diluted with ether and the precipitates were removed by filtration. The filtrate was washed with brine. The residue was dissolved in hexane-AcOEt (4 : 1) and subjected to column chromatography on silica gel. Elution with hexane-AcOEt (4 : 1) gave the coupling product (**2**).[1] *N* -methylphenanthridin-6(5*H*)-one (**2a**), mp 107-108.5˚C (hexane) (lit.,[5] 110-111˚C), (87% from **1a** and 84% from **1c**) and 8-methoxy-*N*-methylphenanthridin-6(5*H*)-one (**2b**), mp 131-133˚C (hexane) (lit.,[1b] 134-134.5˚C) (93% from **1b**).

Coupling Reaction of 6-[(Trifluoromethanesulfonyl)oxy]-2,3-dimethoxy-*N*-methyl-*N*-(6,7-methylenedixoy-1-naphthyl)benzamide (3)

The reaction of **3** (100 mg, 0.2 mmol) with $Pd(OAc)_2$ (4.3 mg, 0.02 mmol), DPPP (8.8 mg, 0.02 mmol), Bu_3P (4.8 μg, 0.02 mmol), and DBU (59 μg, 0.4 mmol) in dry DMF (8 mL) was carried out for 45 min under reflux. The reaction mixture was diluted with ether 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 (2 : 1) gave oxychelerythrine (**4**) (38.4 mg, 54%), mp 194-197˚C (lit.,[6] 199-203˚C), and successive elution with the same solvent gave the starting material (**3**) (29.4 mg, 30%).

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4 In this connection, Pd-catalyzed reaction of **1a** using DABCO in place of DBU for 3 h gave *N*-methylphenanthridone (**2a**) (37 %) and the starting material (**1a**) (57 %).

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