STUDIES ON SUZUKI COUPLING REACTIONS OF LARGE STERICALLY HINDERED SUBSTRATES

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ARTICLE DETAILS

ABSTRACT

Suzuki coupling reaction of 2-(Trifluormethoxy) phenylboronic acid with 2-bromo-1,3-dichloro-5-nitrobenzene were successfully conducted by using $Pd_2(dba)_3$ as the catalyst and in satisfactory to good yields. The 4-(2-(diphenylphosphino)phenyl) morpholine was the best ligand in this reaction. Biaryl amides **8t** which gained much attention in the pharmaceutical industry because of using as $ROR\gamma t$ inhibitors could be synthesized using the product of Suzuki reaction 3a as the substrate after 2 steps. Higher yield of 8t could be got by using this method than the previous work.

KEYWORDS

1. INTRODUCTION

Palladium-catalyzed coupling reactions are becoming a valuable tool in the synthesis of carbon-carbon and carbon-heteratom bonds in modern chemistry [1-3]. These reactions are widely applied in pharmaceutical intermediates, polymer functional materials, pesticides, dyes and organic electroluminescent materials [4-12]. Particularly, Over 60% of the carbon-carbon bond-forming processes in medicinal chemistry are now accomplished using the Suzuki cross-coupling reaction because of its low toxicity, high-efficiency good functional group tolerance and mild reaction conditions [13, 14]. However, the low yields could be received when using large sterically hindered and macromolecule substrates in Suzuki coupling reaction. Recently, N-(2,6-dichloro-2'-(trifluoromethoxy)biphenyl-4-yl)-2-(4-(ethylsulfonyl)phenyl)acetamide (**8t**), which synthesized by 2-(trifluoromethoxy) phenylboronic acid (**1a**) and N-(4-bromo-3,5-dichlorophenyl)-2-(4-(ethylsulfonyl)phenyl) acetamide (**4t**) was reported (see Figure. 1) [15]. Low yield (20%) and the unobtainable substrate (**4t**) limited the application of **8t** which was used as the $ROR\gamma t$ inhibitors.
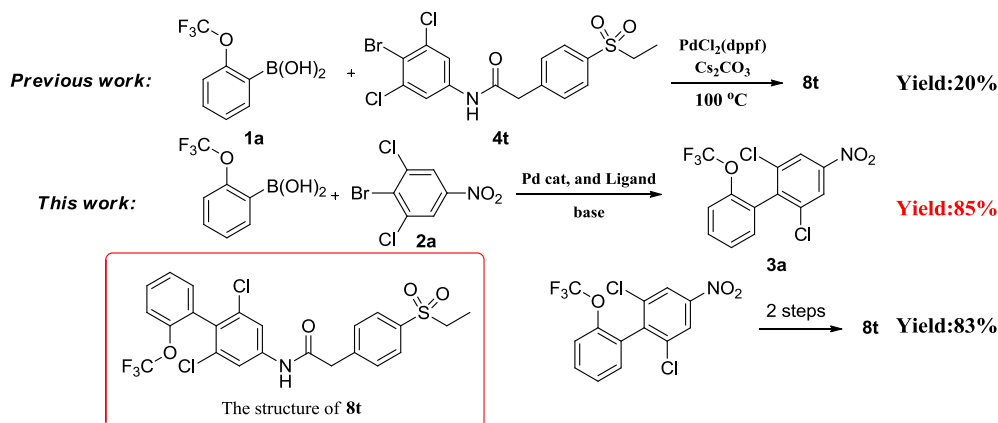

Figure 1: Pd-catalyzed Suzuki coupling reactions for *synthesis* compound 8t

Herein, we report the Suzuki coupling reaction of 2-(Trifluormethoxy) phenylboronic acid with 2-bromo-1,3-dichloro-5-nitrobenzene which were successfully conducted by using $Pd_2(dba)_3$ as the catalyst and 4-(2-(diphenylphosphino)phenyl)morpholine (**L1**) as a ligand to get the product 2,6-dichloro-4-nitro-2'-(trifluoromethoxy)-1,1'-biphenyl (**3a**) in satisfactory to good yields [16,17]. Based on **3a** as the substrate, **8t** could be received. Remarkable, higher yield (more than 70%) could be got of **8t** which proceed after 3steps by using this method (see Figure 1).

2. RESULT AND DISCUSSION

In the initial study, the reaction of 1a with 2a in the presence of Pd catalysts, ligands and base was selected as a model for the optimization of reaction conditions (Table 1). A series of palladium precatalysts, including $PdCl_2$, $Pd_2(dba)_3$, $Pd(OAc)_2$, and $Pd(PPh_3)_4$ were initially tested in the tetrahydrofuran (THF) at 60 °C by using triphenylphosphine (PPh_3) and potassium carbonate (K_2CO_3) as a ligand and a base, respectively (entries 1–4). Among the palladium precatalysts tested, $Pd_2(dba)_3$ exhibited a highest catalytic activity, affording the benzyl but-3-enoate 3a) in 60%

yield (entry 2). No reaction was observed when no ligand was added, suggesting that the ligand was necessary (entries 5). As expected, the use of sterically bulky *P*-ligands (L1, DPPF, DPPB) led to the occurrence of the desired product in 15-85% yields (entries 6–8). The more sterically bulky *P*-bidentate ligand L1 proved to be the best ligand (entries 6). But, no reaction was observed when using dipyridyl as the *N*-bidentate ligand (entries 9). We screened several base (K$_2$CO$_3$, Cs$_2$CO$_3$, and NaOH) to determine a suitable base (entries 6, 10, and 11). These results indicated

that K$_2$CO$_3$ is the most suitable base for the reaction. The yield of 3a decreased to 66% when the reaction was performed under 50 °C (entries 12). Further studies revealed that the similar yield of product 3a was obtained when the reaction temperature was enhanced to 70 °C or the reaction time up to 1.5 h, respectively (entries 13 and 14). A slightly decreased yield was obtained when the reaction was performed under 0.5 h (entries 15)

**Table 1:** Reaction condition screening of Suzuki [a]
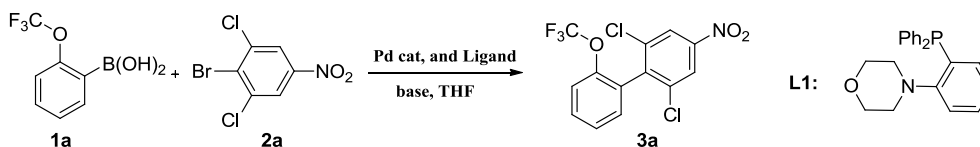
entry	catalyst	ligand	base	yield (%)[b]
1	PdCl$_2$	PPh$_3$	K$_2$CO$_3$	7
2	Pd$_2$(dba)$_3$	PPh$_3$	K$_2$CO$_3$	60
3	Pd(OAc)$_2$	PPh$_3$	K$_2$CO$_3$	18
4	Pd(PPh$_3$)$_4$	—	K$_2$CO$_3$	52
5	Pd$_2$(dba)$_3$	—	K$_2$CO$_3$	0
6	Pd$_2$(dba)$_3$	L1	K$_2$CO$_3$	85
7	Pd$_2$(dba)$_3$	DPPF	K$_2$CO$_3$	20
8	Pd$_2$(dba)$_3$	DPPB	K$_2$CO$_3$	15
9	Pd$_2$(dba)$_3$	dipyridyl	K$_2$CO$_3$	0
10	Pd$_2$(dba)$_3$	L1	Cs$_2$CO$_3$	71
11	Pd$_2$(dba)$_3$	L1	NaOH	50
12[c]	Pd$_2$(dba)$_3$	L1	K$_2$CO$_3$	66
13[d]	Pd$_2$(dba)$_3$	L1	K$_2$CO$_3$	84
14[e]	Pd$_2$(dba)$_3$	L1	K$_2$CO$_3$	85
15[f]	Pd$_2$(dba)$_3$	L1	K$_2$CO$_3$	80

[a] Reaction conditions: (2-(trifluoromethoxy) phenyl)boronic acid 0.5 mmol, 2-bromo-1,3-dichloro-5-nitrobenzene 0.5 mmol, ligand (10 mol%), Pd catalyst (5 mol%), base (2 equiv), THF (5 mL) at 60 °C for 1 h. [b] Isolated yield. [c] the reaction was performed for 50 °C. [d] The reaction was performed at 70 °C. [e] The reaction was performed for 1.5 h. [f] The reaction was performed for 0.5 h.

3. APPLICATION OF THE COMPOUND 3a

Biaryl amides 8t has gained much attention in the pharmaceutical industry because of using as RORγt inhibitors. Compound 3a was further transformed into 2,6-dichloro-2'-(trifluoromethoxy)-[1,1'-biphenyl]-4-amine (4a) in the presence of 0.5 MPa H$_2$ by gold nanopore (AuNPore) as a catalyst under room temperature for 2 h in 87% yield [18]. Then, acylation reaction was generated between 4a and (2-(4-(ethylsulfonyl)phenyl)acetyl)oxonium in the presence of *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC) and 1-Hydroxybenzotriazole (HOBt) in 95% yield (see Figure. 2). The total yield of 8t from 3a was 83%, so this method is better than the previous work.
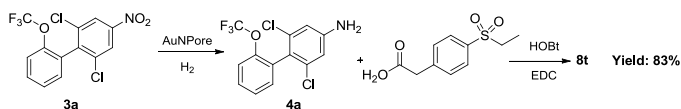
Figure 2: The synthetic procedure of compound 8t

4. CONCLUSIONS

In summary, we developed a novel method for Suzuki coupling of large sterically hindered and macromolecule substrates in a good yield. Notably, this transformation offers a general process for converting the product 3a of the Suzuki reaction into potentially useful compound **8t** in a excellent yield which higher than the previous work. Further reactions and mechanistic studies of **L1** are underway in our laboratory and will be reported in due course.

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APPENDIXES

Representative experimental procedure for the Suzuki coupling reaction

An oven-dried reaction tube (25 mL), fitted with magnetic stirrer, was charged with $Pd_2(dba)_3$ (22.9 mg, 0.025 mmol), K_2CO_3 (13.82 mg, 1.0 mmol), ligand **L1** (17.35 mg, 0.05 mmol), 2-(Trifluormethoxy)phenylboronic acid (95 mg, 0.5 mmol) and 2-bromo-1,3-dichloro-5-nitrobenzene (135.5 mg, 0.5 mmol). The tube was evacuated and purged with nitrogen for three times. Then, freshly distilled THF (5 mL) was added. The reaction mixture was heated to 60 ºC for 1 h. After the reaction completed, the resultant mixture was evaporated in a vacuum to give the crude product, which was then purified via chromatography (eluent: ethyl acetate/petroleum ether = 1:20) to afford product **3a** as a yellow solid.

Synthetic procedure for the compound 8t

The first step: a 25 mL oven dried autoclave vessel containing a stir bar was charged with **3a** (175.5 mg, 0.5 mmol) and AuNPore (5.0 mg, 5 mol%). The autoclave was evacuated and purged with nitrogen for three times. Then, triethylamine (5 mL) and H_2 (1.0 MPa) were added. The reaction mixture was stirred at room temperature for 2 h. Then the remaining H_2 was vented slowly. The resultant mixture was evaporated in vacuo to give the crude product, which was then purified via silica gel chromatography (eluent: ethyl acetate/petroleum ether = 1:2) to afford **4a** as light yellow oil.

The second step: An oven-dried reaction tube (25 mL), fitted with magnetic stirrer, was charged with **4a** (160.5 mg, 0.5 mmol), (2-(4-(ethylsulfonyl)phenyl)acetyl)oxonium (114.0 mg, 0.5 mmol), HOBt (101.3 mg, 0.75 mmol) and EDC (116.4 mg, 0.75 mmol). The tube was evacuated and purged with nitrogen for three times. Then, freshly distilled dichloromethane (5 mL) was added. The reaction mixture was stirred at room temperature for 1 h.. After the reaction completed, the resultant mixture was evaporated in a vacuum to give the crude product, which was then purified via chromatography (eluent: ethyl acetate/petroleum ether = 1:2) to afford product **8t** as a yellow solid.

¹H NMR of 8t

^{1}H NMR (400 MHz, $CDCl_3$) spectra of the products **8t**: δ ppm 7.89 (d, J = 8.0 Hz, 2H), 7.67 (s, 2H), 7.55 (d, J = 8.0 Hz, 2H), 7.48 (m,1H), 7.37 (m, 2H), 7.25 (m, 2H), 3.84 (s, 2H), 3.15 (q, J = 7.6, 7.2 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H).