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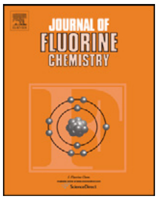

# Pd-catalyzed direct arylation of phenylpyrazole: Synthesis of fipronil derivatives with aryl boronic acids promoted by a stoichiometric amount of NIS

Ting Lv [a], Xiao-Hong Zhang [a,*], Jiang-Sheng Han [a], Ping Zhong [a,b,**]

[a] College of Chemistry and Materials Science, Wenzhou University, Wenzhou 325035, China
[b] Oujiang College, Wenzhou University, Wenzhou 325035, China

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ABSTRACT

The palladium-catalyzed direct arylation of phenylpyrazole with aryl boronic acid promoted by a stoichiometric amount of NIS has been reported. Several phenyl pyrazoles, especially for those with trifluoromethyl groups, can participate in the reaction, providing a series of fipronil derivatives of 4-aryl-phenylpyrazole with potential bioactivity in moderate to good yields. All the compounds were characterized by $^1H$ NMR, $^{13}C$ NMR and HRMS spectroscopic techniques.

## 1. Introduction

Phenyl pyrazole is an important class of heterocyclic compounds and has shown a wide range of biological activities [1]. In addition, phenyl pyrazole derivatives possessing fluorine-containing groups, for example, fipronil (**I**, Fig. 1) [5-amino-1-[2,6-dichloro-4-(trifluoromethyl)-phenyl]-4-trifluoromethylsulfinyl-lH-pyrazole-3-carbonitrile] and ethiprole (**II**, Fig. 1), with 4-EtSO replacing with the 4-$CF_3SO$, are effective against a host of insect pests of crops including grass hoppers, boll weevils, rice insects, termites, houseflies, fruitflies and thrips [2]. The new analog of desulfinylethiprole (**III**, Fig. 1) was surprisingly found to have high insecticidal activity [3]. So we believe that 4-aryl-1-phenylpyrazole compounds (**IV**, Fig. 1) may have the same high insecticidal activity. However, there are relatively few reports for the synthesis of compounds **IV** [4], which was synthesized mainly via the reaction of 4-iodo-1-phenylpyrazole with arylboronic acid [5]. This method requires to prepare substrates to form the electrophiles, and the overall process is neither atom-economical nor green. Therefore, the protocol for novel procedures for the synthesis of 4-aryl-1-phenylpyrazoles containing $CF_3$ group is still a great challenge.

Recently, great interests have been aroused to develop mild methods for the direct functionalization of C–H to construct C–C [6], C–N [7], C–O [8] and C–S [9] bonds. It is well known that Suzuki–Miyaura reaction is one of the most attractive methods to construct C–C bond [10]. With the development of the Suzuki–Miyaura reaction, boronic acids have been developed as powerful reagents owing to their nontoxicity, stability and compatibility with most functional groups [11]. So we envisioned that 4-aryl-1-phenylpyrazoles can be obtained through the metal-catalyzed direct arylation of phenylpyrazoles with aryl boronic acids. And it is very fortunate that the direct arylation of phenylpyrazole occurred smoothly using $PdCl_2(PPh_3)_2$ as catalyst. Here, we describe the novel synthesis of 4-aryl-1-phenylpyrazole derivatives containing $CF_3$ group. All the compounds were characterized by $^1H$ NMR, $^{13}C$ NMR and HRMS spectroscopic techniques.

## 2. Results and discussion

We choose the reaction of 5-amino-1-[2,6-dichloro-4-trifluoromethylphenyl]-l-H-pyrazole-3-carbonitrile (**1a**) with phenyl boronic acid (**2a**) as a model system to determine the optimal reaction conditions (Table 1). Initially, a series of Pd catalysts, including $PdCl_2$, $Pd(OAc)_2$, $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$, were tested for the reaction using 2 equiv $NaHCO_3$ as base, 1 equiv NIS as iodine source, $C_2H_5OH:H_2O$ (3:1) as solvent at 80 °C under $N_2$ (entries 1–4). Among these catalysts screened, $PdCl_2(PPh_3)_2$ showed the

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* Corresponding author. Tel.: +86 0577 86689338; fax: +86 0577 86689338.
** Corresponding author at: College of Chemistry and Materials Science, Wenzhou University, Wenzhou 325035, China. Tel.: +86 0577 86689338;
fax: +86 0577 86689338.
*E-mail addresses:* kamenzxh@163.com (X.-H. Zhang), zhongp0512@163.com (P. Zhong).

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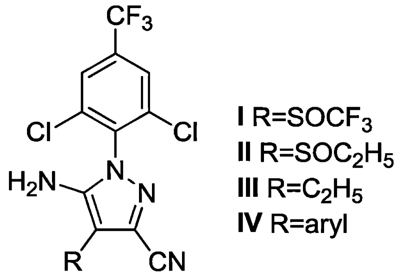


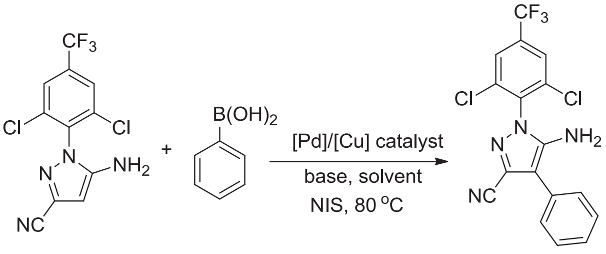
**Fig. 1.** Fipronil (**I**) and analogs (**II**, **III**, **IV**).

highest efficiency. However, when the reaction was conducted under atmospheric condition, the yield was decreased to 54% (entry 3). Other transition-metal catalyst, $Cu(OAc)_2$ was also measured and the byproduct of 4-iodo-1-phenylpyrazole was found to be obtained in a high yield (entry 5). Next, $NaHCO_3$ was replaced with different bases, such as $CH_3ONa$, $Cs_2CO_3$, $K_2CO_3$, t-BuOK, $Na_2CO_3$ and $CH_3COOK$, the results indicated that the identity of base was critical to the success of the direct arylation (entries 6–11). Subsequently, when the amount of $NaHCO_3$ was decreased to 1.5 equiv, the yield of **3** was reduced to 50% (entry 3). Promoted by the help from NIS, other iodide reagents, such as $I_2$ or ICl, were investigated in the presence of $PdCl_2(PPh_3)_2$ and they are less effective than NIS (entries 12–13). Based on our previous work [12], we think NIS promoted the generation of 4-iodo-1-phenylpyrazole in situ compared to $I_2$ and ICl, which was then reacted with phenyl boronic acid to give the arylated product **3**. It is noteworthy the slightly excess of NIS affected the yield slightly, but only 75% yield of **3** was obtained when decreasing the amount of NIS to 0.9 equiv (entries 14–15). It was interesting that no arylated product but only the by-product 4-iodo-1-phenylpyrazole can be obtained in high yields (entries 16–17) when the mixture solvent of $C_2H_5OH:H_2O$ was replaced with $C_2H_5OH$ and dioxane.

With the optimal catalytic system in hand, the scope of boronic acids in the reaction with **1a** was next investigated (Table 2). Gratifyingly, aryl boronic acids with electron-rich and electron-poor groups were successfully converted to the corresponding arylated products in moderate to good yields. Generally speaking, the electron-donating groups, such as methoxy, methyl and ethyl, on the phenyl ring of boronic acids were beneficial for the transformation (entries 2–4), whereas electron-withdrawing groups like chloro, fluoro and trifluoromethyl, decreased the efficiency (entries 7–9). Yet, steric hindrance affected the efficiency. For example, 88% yield of compound **4** without ortho substituent was isolated, while the yield of compounds **7** and **8** derived from ortho-substituted boronic acid were decreased to 69% and 60%, respectively (entries 5–6).

Subsequently, the substrate scope was extended to 5-amino-1-[2-chloro-4-trifluoromethylphenyl]-l-H-pyrazole-3-carbonitrile (**1b**) and 5-amino-1-phenyl-3-methylpyrazole (**1c**). With the strong electron-withdrawing group of trifluoromethyl on the phenyl ring, substrate **1a** and **1b** reacted with aryl boronic acids smoothly to give the arylated products in good yields (entries 1–10). However, when $CF_3$ on the phenyl ring of substrate **1c** disappeared, as well as $CH_3$ instead of CN on the pyrazole ring, no more than 62% of arylated products can be obtained (entries 11–18). The relatively poor reactivity may largely attribute to absence

**Table 1**
Optimization of the arylation conditions.[a]



**1a** **2a** **3**

| Entry | Catalyst | Base | Iodide source | Solvent | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | $PdCl_2$ | $NaHCO_3$ | NIS | $C_2H_5OH:H_2O$ | 25 |
| 2 | $Pd(OAc)_2$ | $NaHCO_3$ | NIS | $C_2H_5OH:H_2O$ | 8 |
| 3 | $PdCl_2(PPh_3)_2$ | $NaHCO_3$ | NIS | $C_2H_5OH:H_2O$ | 85 (50[c], 54[d]) |
| 4 | $Pd(PPh_3)_4$ | $NaHCO_3$ | NIS | $C_2H_5OH:H_2O$ | 52 |
| 5 | $Cu(OAc)_2$ | $NaHCO_3$ | NIS | $C_2H_5OH:H_2O$ | 90[d] |
| 6 | $PdCl_2(PPh_3)_2$ | $CH_3ONa$ | NIS | $C_2H_5OH:H_2O$ | 36 |
| 7 | $PdCl_2(PPh_3)_2$ | $Cs_2CO_3$ | NIS | $C_2H_5OH:H_2O$ | 6 |
| 8 | $PdCl_2(PPh_3)_2$ | $K_2CO_3$ | NIS | $C_2H_5OH:H_2O$ | 32 |
| 9 | $PdCl_2(PPh_3)_2$ | t-BuOK | NIS | $C_2H_5OH:H_2O$ | 30 |
| 10 | $PdCl_2(PPh_3)_2$ | $Na_2CO_3$ | NIS | $C_2H_5OH:H_2O$ | 20 |
| 11 | $PdCl_2(PPh_3)_2$ | $CH_3COOK$ | NIS | $C_2H_5OH:H_2O$ | 19 |
| 12 | $PdCl_2(PPh_3)_2$ | $NaHCO_3$ | $I_2$ | $C_2H_5OH:H_2O$ | 36 |
| 13 | $PdCl_2(PPh_3)_2$ | $NaHCO_3$ | ICl | $C_2H_5OH:H_2O$ | 40 |
| 14[e] | $PdCl_2(PPh_3)_2$ | $NaHCO_3$ | NIS | $C_2H_5OH:H_2O$ | 86 |
| 15[f] | $PdCl_2(PPh_3)_2$ | $NaHCO_3$ | NIS | $C_2H_5OH:H_2O$ | 75 |
| 16 | $PdCl_2(PPh_3)_2$ | $NaHCO_3$ | NIS | $C_2H_5OH$ | 96[g] |
| 17 | $PdCl_2(PPh_3)_2$ | $NaHCO_3$ | NIS | Dioxane | 93[g] |

[a] Reaction conditions: 1a (0.2 mmol), 2a (0.4 mmol), [NIS, $I_2$ or ICl] (1 equiv), [Pd] or [Cu] (10 mol%), base (0.4 mmol), $C_2H_5OH:H_2O$ (3:1), $N_2$, 80 °C for 18 h.
[b] Isolated yield.
[c] $NaHCO_3$ (0.3 mmol).
[d] Without $N_2$.
[e] NIS (1.1 equiv).
[f] NIS (0.9 equiv).
[g] The yield of by-product 4-iodo-1-phenylpyrazole