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Regioselective palladium-catalyzed Suzuki–Miyaura coupling reaction of 2,4,6-trihalogenopyrido[2,3-*d*]pyrimidines

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ABSTRACT

An effective, regioselective, and novel strategy to the access of 2,4,6-trisubstituted pyrido[2,3-*d*]pyrimidines is developed from the corresponding 2,4,6-trihalogenopyrido[2,3-*d*]pyrimidine through a Suzuki–Miyaura coupling reaction involving a novel regioselective halogen discrimination.

1. Introduction

The evolution and continuous discovery of the Pd-catalyzed cross-coupling reactions [1] greatly helped to form and synthesize highly arylated heterocycles. As a result, heterocyclic scaffolds with various functions, which can be alternated into a variety of functionalized heterocycles by using regioselective and efficient reactions, have become more attractive [2].

In the search for novel biocompatible heterocycles with nitrogens, pyridopyrimidine appears to be a very important molecule. Inclusion of this heterocycle in more complex structures has guided to a diverse interval of molecules that can be useful as antibacterial [3], antifolate [4], anti-inflammatory [5], antiviral [6], antimicrobial [7] and anti-cancer agents [8]; antihypertensives [9]; antileishmanials [10]; anticonvulsants [11]; potassium diuretics and preservatives [12]; antiaggressives [13]; and tyrosine kinase [14] and antitumor derivatives [15] with selective proapoptotic activity [16]. This shows the interest of chemists in developing versatile methods for obtaining and functionalizing this heterocycle [17].

Because of our experience with these heterocycles [18], we decided to use this methodology to access the trisubstituted pyrido[2,3-*d*]pyrimidines at positions C2, C4, and C6 in the isomeric position by Suzuki–Miyaura coupling reactions (Scheme 1). Herein, we report the preparation of new trihalogen derivatives **6** and **7** and both regioselectivity functionalized by two different classes of reactions.

2. Results and discussion

The trichlorination of heterocycles has been observed with pyrido[3,2-*d*]pyrimidine [19] and quinazoline [20,21]; however, to our knowledge, the direct trichlorination in a single step of pyrido[2,3-*d*]pyrimidine has not yet been described. We, therefore, performed a halogenation of nicotinic acid before obtaining the final trihalogenated intermediate by cyclization and chlorination.

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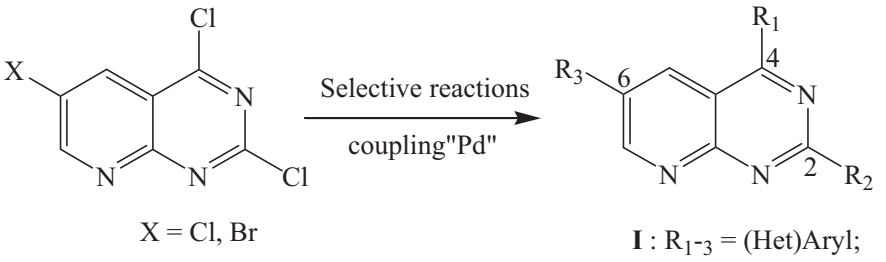
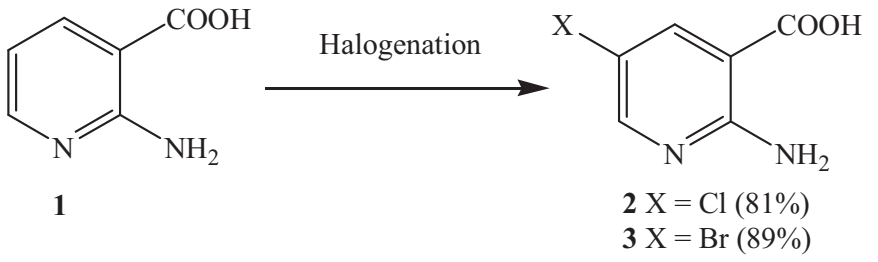


Scheme 1. Strategy.



Scheme 2. Halogenation of 2-aminonicotinic acid at position C5.

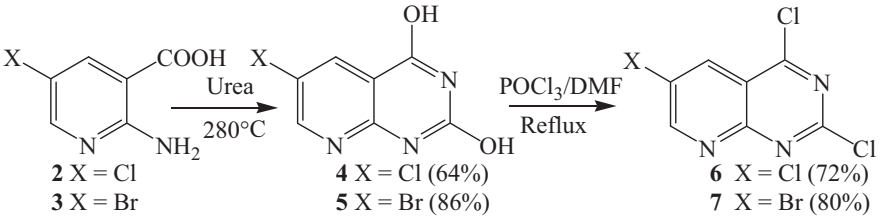
The halogenation of 2-aminonicotinic acid is now well known [22]. It involves the reaction of chlorine or bromine with 2-aminonicotinic acid in acetic acid medium (Scheme 2) [23].

The cyclization and chlorination of the halogenated 2-aminonicotinic acid has been previously described by reaction with urea for cyclization and $POCl_3$ for chlorination [18c].

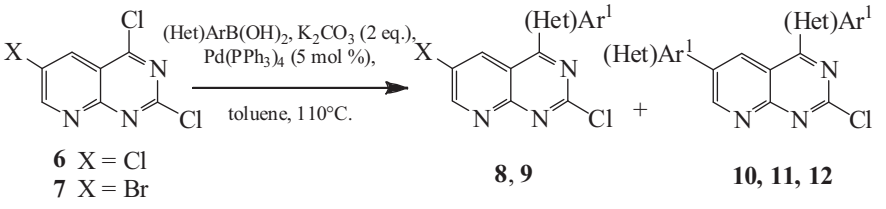
Products **2** and **3** were heated to 280 °C in the presence of urea to yield compounds **4** and **5** with good yields [24]. Chlorination at positions C2 and C4 was then performed using phosphorus oxychloride and a few drops of DMF at reflux to give intermediates **6** and **7** in good yields (Scheme 3) [25].

Compounds **6** and **7** were first engaged in a Suzuki coupling reaction [26]. Then, we carried out a regioselective arylation at C4, by reacting the dichloride compound **6** with 1 equiv of *p*-methoxyphenylboronic acid using 5 mol % of $Pd(PPh_3)_4$, potassium carbonate, and toluene as solvent under reflux (Scheme 4). After completion of the reaction, the monoarylated derivative **8** was obtained in a good yield (83%) (Table 1, entry 1).

For compound **7**, a mixture of monoarylated **9** and biarylated **10** was obtained in a relatively low global yield (43%) (Table 1, entry 2). Therefore, we chose to treat compound **7** with 2 equiv of boronic acid to produce the diarylated products (Table 1, entries 3–5) [27]. The heteroaryl (Het)Ar^1 was introduced and the diarylated products were



Scheme 3. Cyclization and halogenation of compounds **2** and **3**.



Scheme 4. Trihalogenated pyridopyrimidines **6** and **7** (Het)arylation.

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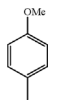
Table 1
Reactivity of halogenated products **6** and **7** with different boronic acids.

Entry	X	Ar^1	Amount of boronic acid (equiv)	Substitution (yields, time)[a]	
				At position C4	At positions C4 and C6
1	Cl		1	**8** (83%, 3 h)	–
2	Br		1	**9** (7%, 3 h)	**10** (36%, 3 h)
3	Br		2	–	**10** (76%, 3 h)
4	Br		2	–	**11** (71%, 3 h)
5	Br		2	–	**12** (75%, 3 h)

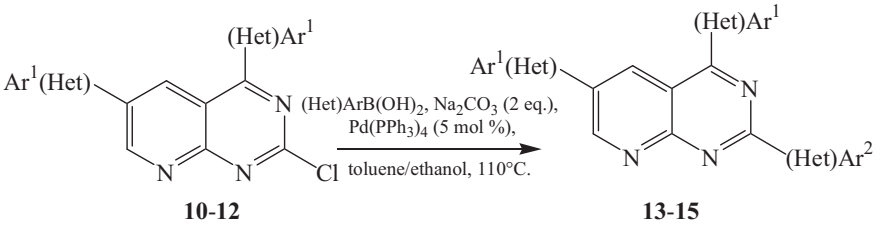
[a] Yield of isolated product. Reaction conditions: $Ar^1B(OH)_2$, K_2CO_3 (1.5 equiv), $Pd(PPh_3)_4$ (5 mol %), toluene, 110 °C.

successfully obtained after purification on silica gel using column chromatography. Compounds **10**–**12** were obtained after 3 h in good yields (71–76%) (Table 1).

Chlorine at position C2 of compounds **10**–**12** was then engaged in a Suzuki coupling and the last (Het)aryl was introduced in the presence of a second boronic acid (Scheme 5, Table 2) [28].

The expected products **13**, **14**, and **15** were obtained after purification on silica gel using column chromatography in good yields of 71%, 67%, and 72%, respectively (Table 2).

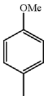
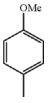
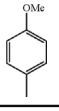
We then engaged compound **8** in a second heteroarylation at the position C2 without any influence on the chlorine atom at position C6. For this second arylation we used ethanol as cosolvent and sodium carbonate as base to achieve the best yield (Scheme 6) [29]. The 3-thienylboronic acid reacted with compound **8** after 2 h to obtain the di(arylated) compound **16** in good yield of 83%.



10-12 **13-15**

Scheme 5. Reactivity of halogenated products **10**–**12** via Suzuki cross-coupling reaction.

Table 2
Heteroarylation of compounds **13**–**15**.

Entry	(Het)Ar^1	(Het)Ar^2	Products	Yield[a] (time)
1			**13**	71% (3 h)
2			**14**	67% (2 h)
3			**15**	72% (2 h)

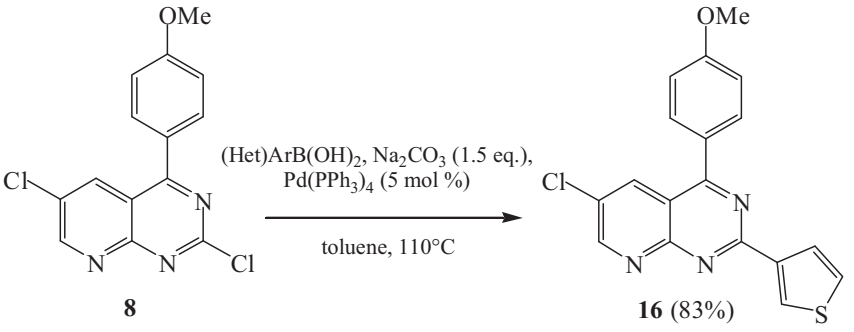
[a] Yield of pure product. Conditions of reaction: $Ar^2B(OH)_2$ (1.05 equiv), Na_2CO_3 (2 equiv), $Pd(PPh_3)_4$ (5 mol %), toluene/ethanol, 110 °C.

We then engaged the compound **16** in a third arylation at the C6 position. The best result was obtained in the presence of sodium carbonate and ethanol as cosolvent (Scheme 7) [29].

The diarylated compound **16** reacted in the presence of 3-furylboronic acid to afford the tri(arylated) compound **17** in only a few hours with good yield of 83%.

Usually the Pd-catalyzed site selective arylation reactions occur first at the more electron-deficient site. The selectivity of the site can be clarified by the fact that position C2 of 2,4,6-trihalogenopyrido[2,3-*d*]pyrimidine is less electron deficient than position C4, and position C6 is less electron deficient than position C2 (Fig. 1) [21,30].

Based on the studies performed by Handy and Zhang [31], we can justify the order and site of the cross-coupling reaction using the ^1H NMR chemical shift values of the parent nonhalogenated heterocyclic compound. Indeed, we



8 **16** (83%)

Scheme 6. Reactivity of halogenated product **24** via Suzuki coupling reaction.

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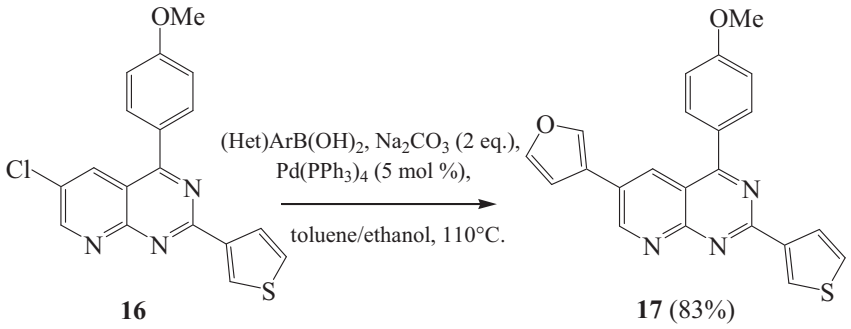

Scheme 7. Reactivity of halogenated product **16** via Suzuki coupling reaction.

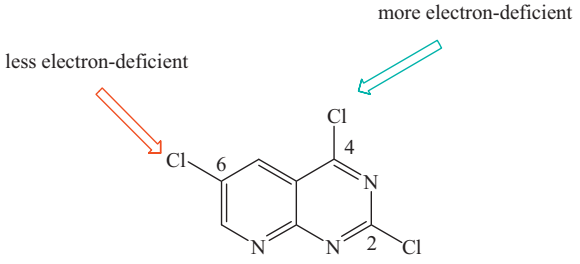

Fig. 1. The site selection process of the palladium-catalyzed coupling reactions of 2,4,6-trihalogenopyrido[2,3-*d*]pyrimidine.

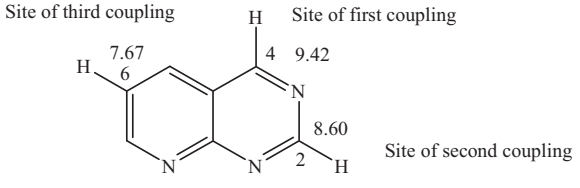

Fig. 2. Suzuki cross-coupling order based upon the ^{1}H NMR chemical shift values.

found that Suzuki coupling reactions were performed successfully in the order C4, C2, and finally C6 (Fig. 2), which means that the carbon with the most deshielded proton is the most reactive carbon.

In this article, we have developed the first access to 2,4-dichloro-6-halogeno-pyrido[2,3-*d*]pyrimidine and its use to prepare two series of substituted pyridopyrimidine using an efficient and novel strategy.

Next, we reported an efficient and simple cross-coupling method for highly trisubstituted-pyrido[2,3-*d*] pyrimidines, which can help in the orchestration of regioselective palladium-catalyzed cross-coupling reactions for the synthesis of focused libraries of biologically active scaffold.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.crci.2019.01.006.

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[23] Procedure for the synthesis of **2** and **3**. 2-Amino-5-chloronicotinic acid (**2**) ($C_6H_5ClN_2O_2$): Acetic acid (200 mL) and water (5 mL) were poured into the solution of 2-aminonicotinic acid 1 (5 g, 36.20 mmol). Chlorine generated by the action of 24 mL of hydrochloric acid and 30 g of KMnO4 was bubbled into the acid suspension. The mixture was reacted for 8 h at room temperature, and then filtered and the solvent evaporated under reduced pressure. The obtained crude material was washed with Et_2O and methanol to give compound **2** as a white solid in 81% yield. 2-Amino-5-bromonicotinic acid (**3**) ($C_6H_5BrN_2O_2$): Acetic acid (250 mL) and water (10 mL) were poured into the solution of 2-aminonicotinic acid 1 (10 g, 72.4 mmol). The suspension was placed at 0°C and Br_2 (4 mL, 79 mmol, 1.1 equiv) was added dropwise. After 8 h of stirring at room temperature, the mixture was filtered and then concentrated under reduced pressure. The crude material obtained was washed with Et_2O to afford compound **3** as a white solid in 89% yield.

[24] Procedure for the synthesis of **4** and **5**. 6-Chloro-1*H*-pyrido[2,3-*d*]pyrimidine-2,4-dione (**4**) ($C_7H_4ClN_3O_2$): The 2-amino-5-chloronicotinic acid 2 (5.96 g, 28.51 mol) was finely ground with urea (13.7 g, 228.1 mmol, 8 equiv). The mixture was heated to the point of evaporation of the urea (280°C) by means of a sand bath until its solidification. After cooling, the solid obtained was dissolved in 500 mL of solution of sodium hydroxide (2 N) and filtered. Then, the filtrate was neutralized with hydrochloric acid solution (6 N) to pH 8 until total precipitation of product. The resultant solid was filtered and then washed with cold water to obtain compound **4** as yellow solid in 64% yield.

[25] Procedure for the synthesis of **6** and **7**. 2,4,6-Trichloro-pyrido[2,3-d]pyrimidine (**6**) (C7H2Cl3N3): A mixture of 50 mL of POCl3, two drops of DMF, and 5 g of 6-chloro-1H-pyrido[2,3-d]pyrimidine-2,4-dione 4 were heated to reflux. After 6 h, the reaction was evaporated under reduced pressure; 400 mL of CH2Cl2 and 20 mL of water were added to the residue at 0°C. The aqueous phase was extracted, the organic layers were combined and then dried over magnesium sulfate. After filtration the filtrate was evaporated under reduced pressure, and then washed with Et2O to obtain compound **6** as a yellow solid in 64% yield.

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[27] Procedure for the synthesis of **8**–**12** via Suzuki cross-coupling reaction: To an argon degassed solution of 6-halogeno-2,4-dichloropyrido[2,3-*d*]pyrimidine **6** or **7** (0.5 mmol) in toluene (6 mL) the desired (Het)aryl boronic acid was added then (1.5 equiv) potassium carbonate and (0.05 equiv) $Pd(PPh_3)_4$ were also added. The reaction was stirred at 110°C for the desired time. After completion of the reaction, 10 mL of water was added, and then extracted with dichloromethane (3 × 10 mL), the organic layers were combined and dried using magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained material was purified on silica gel by column chromatography (CH_2Cl_2/PE: 90/10) to afford compounds **8**–**12**. 2,4-Dichloro-6-(4-methoxyphenyl) pyrido[2,3-*d*]pyrimidine (**8**) ($C_{14}H_9Cl_2N_3O$): Compound **8** was obtained from 2,4,6-trichloropyrido[2,3-*d*]pyrimidine **6** using 4-methoxyphenyl boronic acid (1.05 equiv), as a white solid in 83% yield.

[28] Procedure for the synthesis of **13**–**15** and **17** via Suzuki cross-coupling reaction: Compounds **13**–**15** and **17** were obtained via a Suzuki reaction by reacting compounds **8**–**12** (0.5 mmol) with (het) arylboronic acid (1.05 equiv) in the presence of Na_2CO_3 (2 equiv), $Pd(PPh_3)_4$ (0.05 equiv), and a mixture of toluene/ethanol (3/1) at 110°C. After total completion of the reaction, 10 mL of water and 10 mL CH_2Cl_2 were added. The water layer was extracted with dichloromethane (3 × 10 mL), the organic layers were combined and dried using magnesium sulfate, and then the solvent was evaporated under reduced pressure. The crude material was purified on column chromatography using silica gel (CH_2Cl_2/PE: 90/10) to afford compounds **13**–**15** and **17**.

[29] Procedure for the synthesis of **16** via Suzuki cross-coupling reaction: Compound **16** was obtained via a Suzuki reaction from compound **8** (0.5 mmol) and (het)arylboronic acid (1.2 equiv), in the presence of Na_2CO_3 (1.5 equiv) and $Pd(PPh_3)_4$ (0.05 equiv) in refluxing toluene at 110°C. After complete reaction of compound **8**, 10 mL of water and 10 mL of CH_2Cl_2 were added. Then, the water layer was extracted with dichloromethane (3 × 10 mL), organic layers were combined, dried over magnesium sulfate, and the solvent was removed under reduced pressure. The crude material was obtained by evaporation of solvent under reduced pressure, and then purified by flash chromatography using silica gel (CH_2Cl_2/PE: 90/10) to afford compound **16**.

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