Synthesis of 2-Aryl-3,4,5,6-tetrachloropyridines and 2,6-Diaryl-3,4,5-trichloropyridines by Site-Selective Suzuki–Miyaura Reactions of Pentachloropyridine

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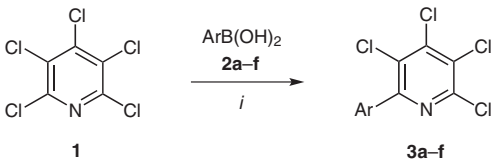
Abstract: The first Suzuki–Miyaura reactions of pentachloropyridine are reported. The reaction with two equivalents of arylboronic acids gave 2,6-diaryl-3,4,5-trichloropyridines, while the reaction with one equivalent of arylboronic acid afforded 2-aryl-3,4,5,6-tetrachloropyridines. The one-pot reaction of pentachloropyridine with two different arylboronic acids resulted in the formation of 2,6-diaryl-3,4,5-trichloropyridines containing two different aryl groups. All reactions proceeded with very good site selectivity.

Key words: catalysis, palladium, Suzuki–Miyaura reaction, pyridine, regioselectivity

Pyridines are of considerable pharmacological relevance and occur in a number of natural products. Examples include nicotinic acid and its derivatives, vitamin B_6, and various other molecules.[1,2] We have recently reported that 2-sulfonylpyridines[3] and 4-hydroxy-4-(pyridyl)alk-3-en-2-ones[4] exhibit antimicrobial activity. Pyridines possess several applications, for example, as drugs, fluorescent chemosensors, and fluorophores.[5] Classic syntheses of pyridines often rely on base-mediated cyclocondensations (e.g., the Hantzsch reaction).[2,6] Despite their great utility, these methods may have drawbacks when specific substitution patterns and labile functionalities are incorporated. To address these limitations, the application of palladium-catalyzed cross-coupling reactions to halogenated pyridines can be advantageous. In recent years, site-selective reactions of polyhalogenated heterocycles have been studied.[7,8] Cross-coupling reactions of 2,5-dibromopyridine include aminations,[9] and Stille,[10] Suzuki,[11] Negishi,[12] Sonogashira,[13] and Kumada couplings.[14] In all cases, the first reaction occurs at the more electron-deficient position C-2. Recently, Handy and co-workers reported the first double Suzuki couplings of 2,5- and 2,3-dibromopyridine.[15] Pentachloropyridine represents an inexpensive and interesting polyfunctionalized substrate. Nucleophilic aromatic substitution reactions of this substrate with O-, N-, and S-nucleophiles have been reported.[16] Only a few reactions with carbon nucleophiles have been studied which include the reaction with enamines[17a] and DMAP.[17b] Metal-halide exchange reactions have also been reported.[18] Palladium-catalyzed cross-coupling reactions of pentahalogenated pyridines have, to the best of our knowledge, not yet been reported. Herein, we report our preliminary results related to Suzuki–Miyaura reactions of pentachloropyridine (**1**). The reactions provide a convenient approach to 2-aryl-3,4,5,6-tetrachloropyridines and 2,6-diaryl-3,4,5-trichloropyridines. These products have only rarely been reported in the literature so far and are not readily available.[19]

Our starting point was to find suitable conditions for the site-selective synthesis of 2-(4-methoxyphenyl)-3,4,5,6-tetrachloropyridine (**3a**) by reaction of **1** with one equivalent of (4-methoxyphenyl)boronic acid (**2a**, Scheme 1). After much optimization (Table 1), we have found that the best conversion and yield were obtained when the reactions were carried out using $Pd(PPh_3)_4$ (5 mol%) as the catalyst and Cs_2CO_3 as the base. The reaction was carried out at 20 °C in a 10:1 mixture of acetonitrile and water (entry 12). Similar results were obtained when toluene was used as the solvent (entry 7). However, the use of K_3PO_4 instead of Cs_2CO_3 proved to be unsuccessful (entry 13, excellent conversion, but low yield). An excess of **2a** (2.2 equiv) had to be employed. The yield decreased when only 1.5 equivalents of **2a** were employed (entry 16). Interestingly, the employment of dry acetonitrile, in the presence of Cs_2CO_3, K_2CO_3, KO*t*-Bu, or K_3PO_4, proved to be unsuccessful in terms of yield (entries 8–11). Moderate yields were obtained when a mixture of toluene and water was used as the solvent (entries 14 and 15). The employment of the monophosphine biaryl ligand X-Phos,[20] which often gives excellent results for Suzuki reactions of aryl chlorides, gave unsatisfactory results (entries 1–6).



1 3a–f

Scheme 1 Synthesis of **3a–f**. *Reagents and conditions*: (*i*) **2a–f** (2.2 equiv), $Pd(PPh_3)_4$ (5 mol%), MeCN–H_2O (10:1), Cs_2CO_3 (1.2 equiv), 20 °C, 20 h.

The reaction of **1** with arylboronic acids **2a–f**, using our optimized conditions (Table 1, entry 12), afforded the 2-aryl-3,4,5,6-tetraarylpyridines **3a–f** in 33–67% yield (Table 2, Scheme 1).[21,22] The best yields were obtained

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Table 1 Optimization of the Synthesis of **3a**

Entry	Catalyst	Solvent	**2a** (equiv)	Temp (°C)	Base	Conversion (**3a**, %)[a]	Yield of **3a** (%)[b]
1	$Pd(OAc_2$/X-Phos	toluene	2.2	80	Cs_2CO_3	55	15
2	$Pd(OAc)_2$/X-Phos	THF	2.2	80	Cs_2CO_3	56	7
3	$Pd(OAc)_2$/X-Phos	dioxane	2.2	80	Cs_2CO_3	68	3
4	$Pd(OAc)_2$/X-Phos	MeCN	2.2	80	Cs_2CO_3	73	28
5	$Pd(OAc)_2$/X-Phos	toluene–THF	2.2	80	Cs_2CO_3	65	20
6	$Pd(OAc)_2$/X-Phos	DMF	2.2	80	Cs_2CO_3	86	7
7	$Pd(PPh_3)_4$	toluene	2.2	20	Cs_2CO_3	88	78
8	$Pd(PPh_3)_4$	MeCN	2.2	20	Cs_2CO_3	74	5
9	$Pd(PPh_3)_4$	MeCN	2.2	20	K_2CO_3	44	5
10	$Pd(PPh_3)_4$	MeCN	2.2	20	KO*t*-Bu	100	15
11	$Pd(PPh_3)_4$	MeCN	2.2	20	K_3PO_4	71	10
12	$Pd(PPh_3)_4$	MeCN–H_2O	2.2	20	Cs_2CO_3	89	79
13	$Pd(PPh_3)_4$	MeCN–H_2O	2.2	20	K_3PO_4	100	33
14	$Pd(PPh_3)_4$	toluene–H_2O	2.2	20	Cs_2CO_3	66	43
15	$Pd(PPh_3)_4$	toluene–H_2O	2.2	20	K_3PO_4	80	46
16	$Pd(PPh_3)_4$	MeCN–H_2O	1.5	20	Cs_2CO_3	95	71

[a] Conversion.
[b] GC-yield (*n*-hexadecane was used as the internal standard).

for the reactions of **1** with (4-methoxyphenyl)boronic acid (**2a**) and for phenylboronic acid (**2e**). The yields decreased when sterically hindered boronic acids (**2b**,**c**) or electron-poor boronic acids (**2d**,**f**) were employed. In all reactions, unreacted starting material was recovered (10–15%). A reaction at position C-6 or at another position was not observed. However, attack at position 6 and formation of 2,6-diaryl-3,4,5-trichloropyridines were observed when the reactions were carried out under more forcing conditions (higher temperature, longer reaction time).

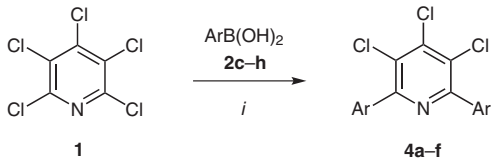
Table 2 Synthesis of **3a–f**

2, **3**	Ar	Yield of **3** (%)[a]
a	4-$MeOC_6H_4$	67
b	2-naphthalene	46
c	2-$MeOC_6H_4$	33
d	4-FC_6H_4	50
e	Ph	62
f	4-$MeCOC_6H_4$	38

[a] Yields of isolated products.

The reaction of **1** with 4.4 equivalents of arylboronic acids **2c–h**, in the presence of $Pd(PPh_3)_4$ (5 mol%) and Cs_2CO_3 (2.4 equiv), afforded the 2,6-diaryl-3,4,5-trichloropyridines **4a–f** in 45–65% yield (Scheme 2, Table 3).[23,24] During the optimization, it proved to be important to use an excess of the boronic acid and to carry out the reaction at 90–100 °C instead of 20 °C. The main side reaction was the formation of biaryls by dimerization of two molecules of the arylboronic acid. In addition, a small amount of unreacted starting material was recovered (<5%).

The second coupling required considerably more forcing conditions compared to the first one. This can be explained by the fact that the presence of an aryl group located at the pyridine moiety results in some deactivation of the pyridine moiety (with regard to the second Suzuki reaction), due to the electron-donating properties of the aryl group.



Scheme 2 Synthesis of **4a–f**. *Reagents and conditions*: (*i*) **2a–f** (4.4 equiv), $Pd(PPh_3)_4$ (5 mol%), MeCN–H_2O (10:1), Cs_2CO_3 (2.4 equiv), 90–100 °C, 20 h.

Table 3 Synthesis of **4a–f**

2	4	Ar	Yield of **4** (%)[a]
c	**a**	2-$MeOC_6H_4$	52
d	**b**	4-FC_6H_4	52
e	**c**	Ph	65
f	**d**	4-$MeCOC_6H_4$	45
g	**e**	3,4-$(MeO)_2C_6H_3$	45
h	**f**	4-MeC_6H_4	62

[a] Yields of isolated products.

The structure of product **4c** was independently confirmed by X-ray crystal structure analysis (Figure 1).[25] The phenyl groups and the pyridine moiety are twisted out of plane.

The one-pot reaction of **1** with two different arylboronic acids afforded the 2,6-diaryl-3,4,5-trichloropyridines **5a–c**, containing two different aryl groups (Scheme 3, Table 4).[26,27] Products **5a** and **5c** were isolated in acceptable yields. The symmetrical products **4** were formed as side products in low yield. In addition, a small amount of starting material was recovered. The yield of 48% of **5c** corresponds to approx. 70% yield per cross-coupling step. The yield of **5b** was relatively low. This can be explained by the fact that an excess of the first boronic acid [4-$(MeO)C_6H_4$] had to be used which is still present in the reaction mixture when the second boronic acid [the rather electron-poor and unreactive boronic acid 4-$(MeCO)C_6H_4$] was added. Therefore, some formation of **4a** as a side product cannot be avoided.

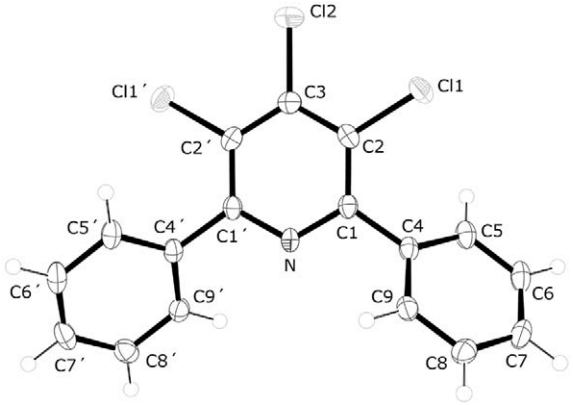
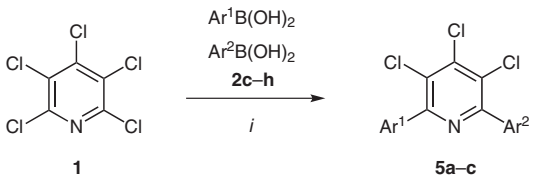


Figure 1 Crystal structure of **4c**



Scheme 3 Synthesis of **5a–c**. *Reagents and conditions*: (*i*) 1) **2a–f** (2.2 equiv), $Pd(PPh_3)_4$ (5 mol%), MeCN–H_2O (10:1), Cs_2CO_3 (2.4 equiv), 80 °C, 2 h; 2) **2a–f** (2.2 equiv), 80 °C, 12 h.

Table 4 Synthesis of **5a–c**

2	5	Ar^1	Ar^2	Yield of **5** (%)[a]
a,**d**	**a**	4-$MeOC_6H_4$	4-FC_6H_4	40
a,**f**	**b**	4-$MeOC_6H_4$	4-$MeCOC_6H_4$	23
f,**h**	**c**	4-$MeCOC_6H_4$	4-MeC_6H_4	48

[a] Yields of isolated products.

In conclusion, we have reported the synthesis of 2-aryl-3,4,5,6-tetrachloropyridines and 2,6-diaryl-3,4,5-trichloropyridines by the first Suzuki–Miyaura reactions of pentachloropyridine. The one-pot reaction of pentachloropyridine with two different arylboronic acids afforded 2,6-diaryl-3,4,5-trichloropyridines containing two different aryl groups. All reactions proceed with very good site selectivity. Our current studies are directed towards functionalization of the remaining chloride groups.

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(21) **General Procedure for the Synthesis of 3a–f**
A solution of $Pd(PPh_3)_4$ (5 mol%, 29 mg), Cs_2CO_3 (1.8 equiv, 290 mg), and pentachloropyridine (0.5 mmol, 126 mg), dissolved in a 10:1 mixture of MeCN (2 mL) and H_2O (0.2 mL) was stirred for 10 min. Subsequently, the boronic acid **2** (2.2 equiv) was added. The solution was stirred for 20 h at r.t. To the reaction mixture was added brine, and the organic and the aqueous layer were separated. The latter was extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4), filtered, and the solution was concentrated in vacuo. The residue was purified by column chromatography (hexane–CH_2Cl_2).

(22) **2,3,4,5-Tetrachloro-6-(4-methoxyphenyl)pyridine (3a)**
Starting with **2a** (1.1 mmol), $Pd(PPh_3)_4$ (5 mol%, 29 mg), Cs_2CO_3 (0.9 mmol, 290 mg), and **1** (0.5 mmol, 126 mg) in MeCN (2 mL) and H_2O (0.2 mL), **3a** was isolated by column chromatography (hexane–CH_2Cl_2 = 4:1) as a white solid (108 mg, 67%), mp 129–130 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.86 (s, 3 H, OCH_3), 6.98 (d, ^3J = 9.0 Hz, 2 H, Ar), 7.70 (d, ^3J = 9.0 Hz, 2 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.4 (OCH_3), 113.6 (CH), 128.1, 128.2, 128.8 ($C_{Ar/Hetar}$), 131.1 (CH), 143.0, 147.1, 154.6, 160.8 ($C_{Ar/Hetar}$). IR (ATR): 3015 (w), 2955 (w), 2923 (w), 2853 (w), 2728 (w), 2553 (w), 1607 (w), 1505 (s), 1350 (m), 1320 (br, s), 1288 (s), 1084 (s), 815 (s) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 323 (100) [M$^+$], 321 (78), 280 (19), 278 (15), 245 (13), 243 (13), 210 (6), 208 (9). HRMS (EI, 70 eV): *m/z* calcd for $C_{12}H_7ONCl_4$: 320.92763; found: 320.927630. Anal. Calcd for $C_{12}H_7Cl_4NO$ (323.0): C, 44.62; H, 2.18; N, 4.34. Found: C, 44.84; H, 2.21; N, 4.33.

(23) **General Procedure for the Synthesis of 4a–f**
A solution of $Pd(PPh_3)_4$ (5 mol%, 29 mg), Cs_2CO_3 (2.4 equiv, 391 mg), and pentachloropyridine (0.5 mmol, 126 mg) in MeCN (2 mL) and H_2O (0.2 mL) was stirred for 10 min at 20 °C. Subsequently, the boronic acid **2** (2.4 equiv) was added at 20 °C. The solution was stirred for 20 h at 90–100 °C. The workup was carried out as described for the synthesis of **3a–f**.

(24) **3,4,5-Trichloro-2,6-diphenylpyridine (4c)**
Starting with $Pd(PPh_3)_4$ (5 mol%, 29 mg), Cs_2CO_3 (1.2 mmol, 391 mg), **1** (0.5 mmol, 126 mg), and **2e** (1.2 mmol, 146 mg) in MeCN (2 mL) and H_2O (0.2 mL), **4e** was isolated as a white solid (109 mg, 65%), mp 168–170 °C; reaction temperature 100 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.40 (m, 2 H, CH), 7.44–7.50 (m, 4 H, CH), 7.61–7.65 (m, 4 H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 127.2, 127.3, 128.8 (CH_{Ar}), 129.7, 141.2, 144.7, 146.5 (C_{Hetar}). IR (ATR): 3058 (w), 2921 (m), 1731 (m), 1529 (s), 1486 (br, s), 1369 (s), 1329 (s), 1297 (s), 1200 (br, s), 1067 (m), 883 (m), 817 (s), 771 (s), 737 (s), 708 (s), 691 (s), 599 (s) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 340 (68) [M]$^+$, 294 (11), 302 (11), 299 (20), 298 (100), 263 (13), 227 (30), 160 (25), 149 (11). HRMS (EI, 70 eV): *m/z* calcd for $C_{17}H_{10}Cl_3N$: 332.98733; found: 332.98738. Anal. Calcd for $C_{17}H_{10}NCl_3$ (334.63): C, 61.02; H, 3.01; N, 4.19. Found: C, 61.35; H, 3.24; N, 3.89.

(25) CCDC-771412 contain all crystallographic details of this publication which are available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ; fax: +44 (1223)336033; or deposit@ccdc.cam.ac.uk.

(26) **General Procedure for the Synthesis of 5a–c**
To a solution of $Pd(PPh_3)_4$ (5 mol%, 29 mg), Cs_2CO_3 (2.4 equiv, 391 mg), and pentachloropyridine (0.5 mmol, 126 mg) in MeCN (2 mL) and H_2O (0.2 mL) was added the first boronic acid (2.2 equiv). The solution was stirred for 2 h at 80 °C. After cooling to r.t., the second boronic acid (2.2 equiv) was added. The solution was stirred for 12 h at 80 °C.

The workup was carried out as described for the synthesis of **3a**–**f**.

(27) **1-{4-[3,4,5-Trichloro-6-(*p*-tolyl)pyrid-2-yl]phenyl}ethanone (5c)**

Starting with **2f** (1.1 mmol, 180 mg), **2h** (1.1 mmol, 150 mg), $Pd(PPh_3)_4$ (5 mol%, 29 mg), Cs_2CO_3 (1.2 mmol, 390 mg), and **1** (0.5 mmol, 126 mg) in MeCN (2 mL) and H_2O (0.2 mL), **5c** was isolated by column chromatography (heptanes–EtOAc = 10:1) as a colorless solid (93 mg, 48%), mp 190–192 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.35 (s, 3 H, CH_3), 2.58 (s, 3 H, CH_3), 7.21 (d, ^3J = 8.3 Hz, 2 H, Ar), 7.57 (d, ^3J = 8.2 Hz, 2 H, Ar), 7.77 (d, ^3J = 8.6 Hz, 2 H, Ar), 7.98 (d, ^3J = 8.6 Hz, 2 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (CH_3), 26.8 (CH_3), 128.0 ($C_{Ar/Hetar}$), 128.1 (CH), 128.3, 128.8, 128.9 ($C_{Ar/Hetar}$), 128.9, 129.4 (CH), 129.6 ($C_{Ar/Hetar}$), 129.9 (CH), 134.7, 137.3, 139.7, 142.2 ($C_{Ar/Hetar}$), 197.7 (C=O). IR (ATR): 3339 (w), 3076 (w), 3031 (w), 2997 (w), 2921 (m), 2853 (w), 1674 (w), 1607 (s), 1523 (m), 1493 (m), 1357 (s), 1267 (s), 1186 (m), 959 (m), 815 (s) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 389 (51) [M^+], 378 (33), 376 (100), 374 (98), 346 (20), 276 (10), 240 (9), 187 (9). HRMS (EI, 70 eV): *m/z* calcd for $C_{20}H_{14}O_1N_1Cl_3$: 389.01355; found: 389.01319.