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# Suzuki–Miyaura coupling of 2-bromopyridine with 2-formylphenylboronic acid

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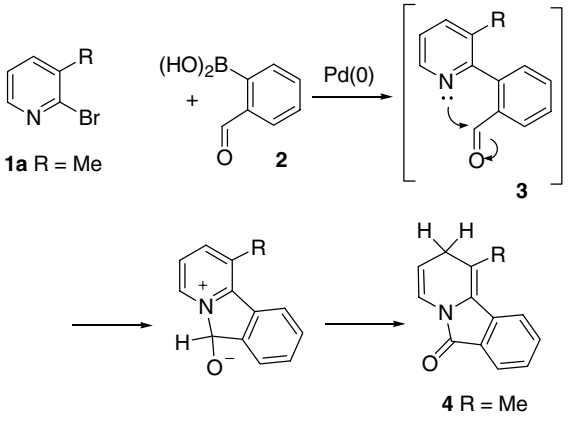
**Abstract**—Suzuki–Miyaura coupling of 2-bromopyridine **1b** with 2-formylphenylboronic acid **2** under standard conditions, gives 2-[4-(2-pyridin-2-yl-benzyl)-pyridin-2-yl]benzoic acid **5b**. A similar reaction is observed for 2-bromo-6-methylpyridine **1c**. A mechanistic rationale for these unusual observations is suggested.

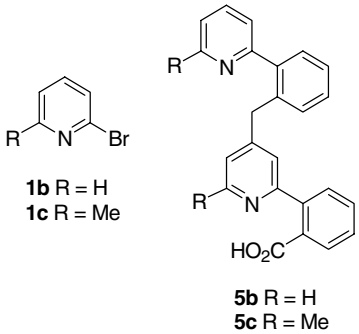

Application of the Suzuki–Miyaura coupling reaction has revolutionized synthetic routes to arylated heterocyclic compounds.[1,2] Although the reaction outcome is usually highly predictable, Mamane and Fort have reported that anomalous products are obtained when certain 2-halogenopyridines [e.g., **1a** (R = Me)] and related heterocycles are coupled with 2-formylphenylboronic acid **2**.[3] The initial coupling product **3** undergoes a cyclization and formal hydride shift to provide pyrido[2,1-*a*]isoindolones **4** (Scheme 1). Other workers have reported very low yields of coupling products in similar reactions.[4]

Here, we show that the palladium-catalyzed reaction of 2-bromopyridine **1b** itself with 2-formylphenylboronic acid **2** produces an unusual dimeric species **5b** whose formation can be rationalized by the involvement of pyrido[2,1-*a*]isoindolone intermediates. A similar reaction is observed for 2-bromo-6-methylpyridine **1c**.




**Scheme 1.**

Thus, Suzuki–Miyaura coupling of 2-bromopyridine **1b** with 2-formylphenylboronic acid **2** under the conditions, which were used to make the 3-isomer[5] gave no product, which could be isolated by the usual work-up, but continuous extraction with dichloromethane over a period of 16 h gave a high yield of a single compound as a foamy solid.[6] Its mass spectrum (FAB conditions) showed a molecular ion (M+1) at *m*/*z* 367 Da indicating that the product bears a dimeric relationship to both aldehyde **3** (R = H) and pyrido[2,1-*a*]isoindolone **4** (R = H). Its NMR spectra ($CDCl_3$) showed that a $CH_2$ group was present ($\delta_H$ 4.19, $\delta_C$ 38.7) and a broad signal at $\delta_H$ 9.95 was observed due to a carboxylic acid function, supported by the presence of a quaternary signal at $\delta_C$ 169.9 in the $^{13}C$ NMR spectrum.

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The structure of this unknown product was established as 2-[4-(2-pyridin-2-yl-benzyl)-pyridin-2-yl]benzoic acid **5b** by the sequence of NMR experiments described below, which were carried out at 600 MHz in [$^2H_6$]acetone solution, the combination of spectrometer frequency and solvent helping to maximize dispersion in the proton dimension (Fig. 1).

The correlation of $^1H$ and $^{13}C$ chemical shift values shown in Table 1 was obtained by a $^1H/^{13}C$ HSQC experiment. A $^1H$ TOCSY experiment permitted the grouping of the $^1H$ signals into spin systems establishing the presence of three 4-spin systems (signals K, L, M and P designated B1; signals D, G, N and R, designated P2; signals E, F, H and J, designated B2) and one 3-spin system (signals B, C and Q designated P1) in addition to the methylene group (signal A, $\delta_H$ 4.29) and that due to the carboxylic acid.

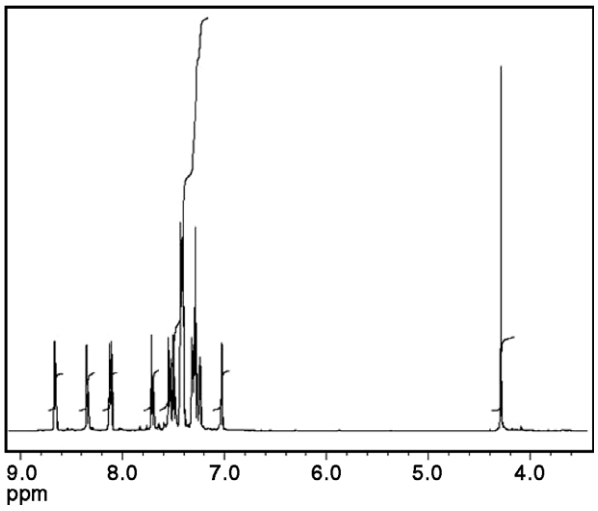
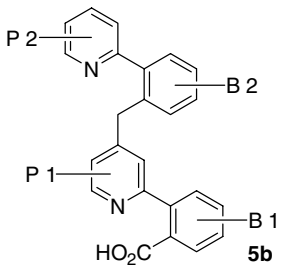



**Figure 1.** $^1H$ NMR spectrum (600 MHz, acetone-$d_6$) of **5b**.

**Table 1.** Correlation of $^1H$ and $^{13}C$ NMR signals of **5b** (600 MHz in [$^2H_6$]acetone)




**5b**

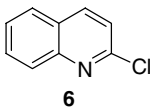
| H-1 Label | $\delta_H$ ($^1H$) | *J*/Hz | $\delta_C$ ($^{13}C$) | Spin system |
|---|---|---|---|---|
| A | 4.29 | s | 37.8 | |
| B | 7.01 | 4.6 | 122.9 | P1 |
| C | 7.27 | s | 123.6 | P1 |
| D | 7.31 | 7.7, 4.9, 1.1 | 122.2 | P2 |
| E | 7.38 | 6.7, 2.5 | 127.2 | B2 |
| F | 7.40 | [a] | 128.6 | B2 |
| G | 7.41 | [a] | 131.0 | P2 |
| H | 7.42 | [a] | 124.3 | B2 |
| J | 7.44 | [a] | 130.3 | B2 |
| K | 7.48 | [a] | 130.3 | B1 |
| L | 7.50 | [a] | 128.2 | B1 |
| M | 7.58 | 7.4, 1.4 | 131.0 | B1 |
| N | 7.80 | 7.7, 1.8 | 136.6 | P2 |
| P | 7.85 | 7.7, 1.1 | 130.3 | B1 |
| Q | 8.36 | 4.9 | 148.3 | P1 |
| R | 8.67 | 4.6 | 148.9 | P2 |

[a] Complex region of overlapping signals.

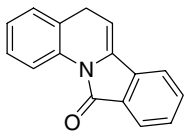
Identification of the components of the 3-spin system P1 suggested that it was likely to be due to a 2,4-disubstituted pyridine unit and a $^1H$ NOESY experiment showed that the methylene group was attached to the 4-position of this pyridine ring (via NOE correlations between signals A and C and also between signals A and B, thereby defining the position of the $CH_2$ with respect to P1). The 2-substituent of the disubstituted pyridine was identified as the 4-spin system B1, from the NOESY relation between signals C and K. Confirmation that the carboxylic acid group was attached to B1 was arrived at from a $^1H/^{13}C$ HMBC experiment, in which correlations were detected between signals K and P (both previously designated B1) and the $^{13}C$ signal at $\delta_C$ 168.9 (corresponding to the carbonyl carbon atom of the carboxylic acid).

A close inspection of the NOESY data reveals a correlation between signals A and F, thereby establishing the P1–$CH_2$–B2 connectivity pathway. The linkage between rings P2 and B2 was confirmed from correlations present in the $^1H/^{13}C$ HMBC experiment, between a quaternary $^{13}C$ signal at $\delta_C$ 159.6 (due to a C2 of the pyridine ring) and $^1H$ signals G (from P2) and H (from B2). Therefore, having established the B1–P1–$CH_2$–B2–P2 linkage, along with the nature and substitution patterns of the precursors, only 2-[4-(2-pyridin-2-yl-benzyl)-pyridin-2-yl]benzoic acid **5b** is consistent with the data.

As a second example, of this dimerization process, reaction of 2-formylphenylboronic acid **2** with 2-bromo-6-methylpyridine **1c** gave the corresponding product **5c** after continuous extraction of the reaction mixture. Reaction of 2-chloroquinoline **6** under our conditions gave **7** as found by Mamane and Fort.[3]

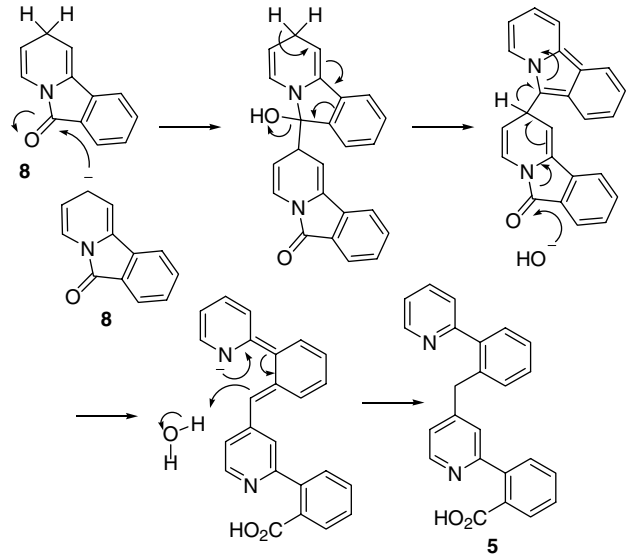



**6**




**7**

A mechanistic scheme for the formation of **5** must explain the concomitant disproportionation of two aldehyde groups and the functionalization of an unactivated pyridine ring in the 4-position by a substituted benzyl group. It is likely that parent pyrido[2,1-*a*]isoindolone **8** (cf. **4**) is an intermediate and a possible rationalization is shown in Scheme 2. Condensation of two molecules of **8** is possible under the basic conditions of the Suzuki–Miyaura coupling. Dehydration, hydride shift (already implicated in the formation of **4**) and rehydration complete the process.



**Scheme 2.**

In conclusion, we have obtained unexpected products under Suzuki–Miyaura coupling conditions when a 2-formylphenyl group is present at a site adjacent to a pyridine-type nitrogen atom. These observations complement those of Mamane and Fort[3] and provide a new, readily available pyridine scaffold for further investigation.

## Acknowledgement

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## References and notes

1. Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Pergamon Press: Amsterdam, 2000.
2. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
3. Mamane, V.; Fort, Y. *Teterahedron Lett.* **2006**, *47*, 2337–2340.
4. Meier, P.; Legraverant, S.; Müller, S.; Schaub, J. *Synthesis* **2003**, 551–554.
5. Sharp, J. T.; O'Shea, D. F. *J. Chem. Soc., Perkin Trans. 1* **1996**, 515–518.

6. *Experimental*: A solution of 2-bromopyridine **1b** (0.30 $cm^3$, 3.16 mmol) and tetrakis(triphenylphosphine)palladium (0.102 g, 0.09 mmol) in ethylene glycol dimethyl ether (15 $cm^3$) was stirred under nitrogen for 20 min. Sodium carbonate (0.437 g, 4.12 mmol), water (15 $cm^3$) and 2-formylphenylboronic acid **2** (0.470 g, 3.14 mmol) were added and the reaction mixture was heated under reflux in the absence of light for 20 h. The solvent was removed from the solution under reduced pressure. The residue was added to water (25 $cm^3$) and small amounts of starting materials were removed by extraction into dichloromethane. After 16 h of continuous extraction of the aqueous phase with dichloromethane a yellow foam was obtained by concentration of the organic extracts, which was identified as *2-[4-(2-pyridin-2-yl-benzyl)-pyridin-2-yl]benzoic acid* **5b**. The yield was dependent on the continuous extraction conditions, but recoveries of up to 94% (0.546 g) have been obtained; [found $(M+H)^+$ 367.1446. $C_{24}H_{19}N_2O_2$ requires *M* 367.1447] $\delta_H$ (250 MHz, $CDCl_3$): 4.19 (2H, s), 6.92 (1H, d, *J* 4.7), 7.23–7.45 (4H, m), 7.30–7.33 (4H, m), 7.40 (2H, m), 7.61 (1H, td, *J* 1.8, 7.4), 8.00 (1H, dd, *J* 1.8, 7.4), 8.24 (1H, d, *J* 5.5), 8.56 (1H, d, *J* 4.4) and 9.95 (1H, br s); $\delta_C$ (63 MHz, $CDCl_3$): 38.7 ($CH_2$), 122.0 (CH), 123.4 (CH), 124.1 (CH), 124.9 (CH), 127.3 (CH), 128.8 (CH), 129.1 (CH), 129.1 (quat), 130.2 (CH), 130.5 (CH), 130.8 (CH), 131.0 (CH), 132.6 (CH), 133.0 (quat), 136.0 (quat), 136.7 (CH), 140.2 (quat), 145.6 (CH), 148.7 (CH), 153.8 (quat), 156.9 (quat), 159.2 (quat) and 169.9 (quat); other data obtained from a [$^2H_6$] acetone solution, are shown in Table 1; *m/z* (FAB) 367 [$(M+H)^+$, 100%].

When these reaction conditions and work-up were repeated using 2-bromo-6-methylpyridine **1c** in place of 2-bromopyridine, *2-{6-methyl-4-[2-(6-methylpyridin-2-yl)-benzyl]-pyridin-2-yl}benzoic acid* **5c** was obtained in 8% yield (found $M^+$ 394.1670. $C_{26}H_{22}N_2O_2$ requires *M* 394.1676) $\delta_H$ (360 MHz, $CDCl_3$): 2.51 (6H, s), 4.24 (2H, s), 6.91 (1H, s), 7.06 (2H, d, *J* 7.8), 7.18 (1H, s), 7.27–7.59 (9H, m) and 8.22 (1H, m); $\delta_C$ DEPT (90 MHz, $CDCl_3$): 23.7 ($2CH_3$), 39.0 ($CH_2$), 122.1 (CH), 122.6 (CH), 123.6 (CH), 124.8 (CH), 128.5 (CH), 129.8 (CH), 130.5 (CH), 131.3 (CH), 131.6 (CH), 132.0 (CH), 132.4 (CH), 135.0 (CH) and 137.9 (CH). *m/z* (EI) 394 ($M^+$, 61%), 349 (59), 278 (51), 259 (86), 199 (51), 55 (79) and 43 (100).

Under similar conditions, 2-chloroquinoline **6** and 2-formylphenylboronic acid **2** provided 5*H*-isoindolo[2,1-*a*]quinolin-11-one[3] **7** as a yellow solid (13%).$\delta_H$ (360 MHz, $CDCl_3$): 3.80 (2H, d, *J* 4.0), 6.03 (1H, t, *J* 4.0, 8.2), 7.09–7.19 (2H, m), 7.30 (1H, ddd, *J* 1.9, 7.2, 8.6), 7.50 (1H, ddd, *J* 1.0, 7.2, 8.6), 7.59 (1H, ddd, *J* 1.0, 7.2, 8.2), 7.68 (1H, ddd, *J* 0.9, 1.9, 7.6), 7.90 (1H, ddd, *J* 0.9, 2.0, 7.6) and 9.00 (1H, dd, *J* 0.9, 8.6); $\delta_C$ (90 MHz, $CDCl_3$): 27.7 ($CH_2$), 103.6 (CH), 117.8 (CH), 119.1 (CH), 121.9 (quat), 123.2 (CH), 124.6 (CH), 127.5 (CH), 128.9 (CH), 129.1 (CH), 130.1 (quat), 131.9 (CH), 133.3 (quat), 133.9 (quat), 135.1 (quat) and 165.1 (quat).