# Pyrrole Acylation for the Synthesis of 2-Bromo-6-(2-pyrrolyl)pyridine and Subsequent Cross-Coupling Reactions

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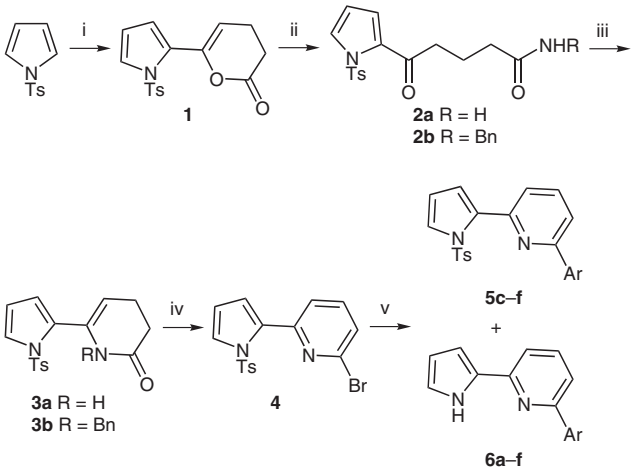
**Abstract:** A facile synthesis of 2-bromo-6-pyrrolylpyridine **4** was developed starting from acylation of pyrrole with glutaric acid and TFAA. Suzuki cross-couplings of **4** with arylboronic acids gave a variety of novel 2-aryl-6-pyrrolylpyridines in excellent yields.

**Key words:** pyrrole acylation, 2-bromo-6-pyrrolylpyridine, 2-aryl-6-pyrrolylpyridines, Suzuki cross-coupling, detosylation

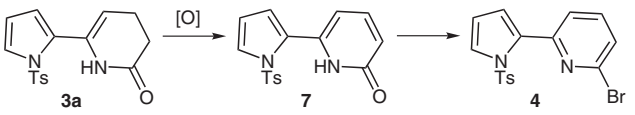
2-(2′-Pyrrolyl)pyridines[1,2] are a useful class of compounds as potential semiconducting materials[3] and metal-binding ligands.[4–14] They have also shown important biological activities.[15–17] The synthesis of these molecules generally falls into two categories, (1) coupling of 2-halopyridines with pyrroles or their organometallic derivatives,[18–26] and (2) formation of the pyrrole ring from a pyridine derivative.[2,3,9,11,14c,d,27–34] To our surprise, strategies using a pyrrole derivative and formation of a pyridine ring are rare,[35–37] and either require usage of special substrates and catalyst, or result in the formation of the desired product in very low yield.

Previously, we developed a new pyrrole acylation method using carboxylic acids and TFAA,[38] and successfully applied this methodology to the synthesis of pyrrolylpyridazines.[39] We now report the application of this methodology for the synthesis of 2-bromo-6-pyrrolylpyridines and the subsequent cross-coupling reactions.

As shown in Scheme 1, treatment of *N*-tosylpyrrole[40] with glutaric acid and TFAA resulted in the formation of dihydropyrone **1** through monoacylation, intramolecular cyclization of the remaining carboxylic acid group onto the ketone function, and dehydration. Reaction of **1** with ammonium acetate or benzylamine gave the ring-opening products **2a**,**b**, which on treatment with PTSA, furnished dihydropyridinone **3a**,**b** in excellent overall yields. Next, transformation of **3a** into 2-bromo-6-pyrrolylpyridine **4** was examined, first following the sequence as shown in Scheme 2. A range of reagents under a variety of conditions were employed for the oxidation of **3a** into pyrrolylpyridinone **7**, including $MnO_2$ in refluxing $CH_2Cl_2$,[41] $SeO_2$ in dioxane at ambient temperature or under reflux,[39] DDQ in toluene at –20 °C, ambient temperature or under reflux,[38] and 10% Pd/C in refluxing toluene.[42] However, only in the case of DDQ as oxidant a small amount (<10% yield) of the desired pyrrolylpyridinone **7** was isolated. No product was produced under other conditions. Oxidation of **3b** under the above conditions also failed to deliver the corresponding pyrrolylpyridinone. The alternative route was then tried, by reacting **3a**,**b** with $POBr_3$ first,[43] followed by oxidation (Scheme 1). To our delight, when dihydropyridinone **3a** was subjected to 15–20 equivalents of $POBr_3$, 2-bromo-6-pyrrolylpyridine **4** was isolated directly in an optimized 35% yield. The same product was obtained when dihydropyridinone **3b** was used as the starting material under the same reaction conditions, but in much higher yield (65%).




**Scheme 1** *Reagents and conditions*: (i) glutaric acid, TFAA, $CH_2Cl_2$, 40 °C, 40 h, 35%; (ii) for the synthesis of **2a**: $NH_4OAc$, EtOH, reflux, 3 h, 98%; for the synthesis of **2b**: $BnNH_2$, toluene, reflux, 1 h, 88%; (iii) PTSA, toluene, reflux, 84% for **2a**, 90% for **2b**; (iv) $POBr_3$, toluene, reflux, 35% for **3a**, 65% for **3b**; (v) $ArB(OH)_2$, $Pd(PPh_3)_4$, $K_2CO_3$, toluene–MeOH, reflux.




**Scheme 2**

Next, the Suzuki cross-coupling reactions[44] of bromopyridine **4** with a variety of arylboronic acids were investigated. Initial attempt was carried out with phenylboronic acid. Under the classic conditions with $Pd(PPh_3)_4$ as cata-

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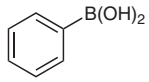
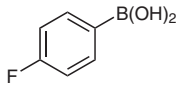
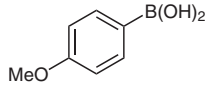
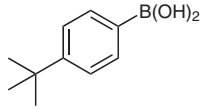
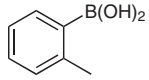
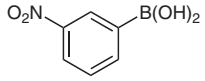
lyst, $K_2CO_3$ as base, cross-coupling reaction between bromopyridine **4** and phenylboronic acid gave, with in situ detosylation, 2-phenyl-6-pyrrolylpyridine (**6a**) in 98% isolated yield. Slightly lower, but still excellent yield (89%) was obtained when $K_3PO_4$ was used as the base. Thus, the first mentioned reaction conditions were employed for the rest of our study without further optimization. The results of cross-coupling reactions with other boronic acids are collected in Table 1.

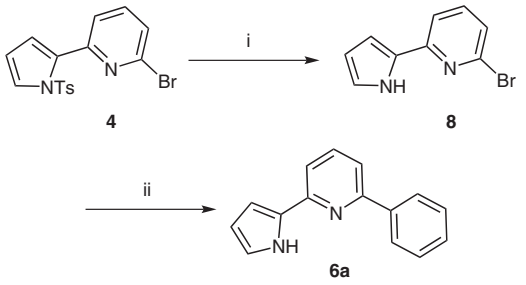
**Table 1** Results of Suzuki Cross-Coupling Reactions of Bromide **4** with Arylboronic Acids [a]

| Entry | Boronic acids | Products | Yield (%) [b] |
|---|---|---|---|
| 1 |  | **6a** (Ar = Ph) | 98 |
| 2 |  | **6b** (Ar = 4-FC$_6$H$_4$) | 92 |
| 3 |  | **5c** (Ar = 4-MeOC$_6$H$_4$)<br>**6c** (Ar = 4-MeOC$_6$H$_4$) | 81<br>trace [c] |
| 4 |  | **5d** (Ar = 4-*t*-BuC$_6$H$_4$)<br>**6d** (Ar = 4-*t*-BuC$_6$H$_4$) | 66<br>27 [d] |
| 5 |  | **5e** (Ar = 2-MeC$_6$H$_4$)<br>**6e** (Ar = 2-MeC$_6$H$_4$) | 44<br>49 [d] |
| 6 |  | **5f** (Ar = 3-O$_2$NC$_6$H$_4$)<br>**6f** (Ar = 3-O$_2$NC$_6$H$_4$) | 57<br>32 [d] |

[a] Bromide **4** /boronic acid/$K_2CO_3$ = 1:1.25:2.5.
[b] Yields obtained after the bromide **4** had completely reacted; typical reaction time 11–15 h, except for entry 2, in which case 23 h was needed for completion of the reaction.
[c] Compound **6c** could be isolated in 71% yield as the sole product when the reaction time was extended to 35 h.
[d] Compounds **6d** – **f** could be isolated as the sole products if large excess (>10 equiv) of base was applied.

Similar to phenylboronic acid (entry 1), cross-coupling reaction of 4-fluorophenylboronic acid with bromide **4** resulted in the formation of detosylated pyrrolylpyridine **6b** as the sole product (entry 2). In all other cases a mixture of compounds **5c–f** and **6c–f** were obtained (entries 3–6), which could be isolated by column chromatography. Compound **5c** was obtained as the major product, together with a small amount (<5%) of **6c**, in the cross-coupling reaction of 4-methoxyphenylboronic acid (entry 3) with bromide **4** after a reaction time of 12 hours. However, **6c** could be isolated in 71% yield as the sole product after prolonged reflux (35 h). For entries 4–6, remarkable amounts of the detosylated products **6d–f** were formed when bromide **4** had completely reacted as indicated by TLC (11–13 h), but the ratio of **5d–f** to **6d–f** did not vary too much after prolonged reflux (35 h). Similar results were obtained when KOH was used as the base. However, if large excess (>10 equiv) of base was applied, compounds **5d–f** could be transformed completely into **6d–f** during the cross-coupling reactions, with much shorter time required for KOH (<10 h) than for $K_2CO_3$ (>30 h). As an example, **6e** could also be obtained in excellent yield by detosylation of **5e** with NaOH in methanol.

Finally, nucleophilic aromatic substitution of the bromide in **4** by sodium methoxide was attempted. However, only the detosylated product **8** was obtained, and the bromide was unaffected (Scheme 3). Suzuki cross-coupling reaction of **8** with phenylboronic acid was also possible and led to the formation of **6a** in 89% isolated yield.




**Scheme 3** *Reagents and conditions* : (i) NaOH, MeOH, reflux, 3.5 h, 63%; (ii) Ph B(OH)$_2$, Pd(PPh$_3$)$_4$, $K_2CO_3$, toluene–MeOH, reflux, 20 h, 89%.

In summary, an efficient synthesis of 2-bromo-6-pyrrolylpyridine **4** based on pyrrole acylation has been developed. Suzuki cross-coupling reactions of compound **4** with arylboronic acids give a variety of novel 2-aryl-6-pyrrolylpyridines in excellent yields. Since acylations of 2-substituted pyrroles with glutaric acid and TFAA are also successful, [38a] this method could potentially be adapted for the synthesis of substituted pyrrolylpyridine derivatives. These are currently under investigation and the results will be published in due course.

Solvents were dried according to standard procedures where needed. Petroleum ether (PE) used refers to the fraction boiling at 60–90 °C. Melting points were measured on a XT4A melting point apparatus and are not corrected. IR spectra were obtained using an IFS25 FT-IR spectrometer. $^1$H and $^{13}$C NMR spectra were obtained on a Bruker AV300 instrument. Mass spectra were recorded on a Micromass Q-TOF mass spectrometer.

**3,4-Dihydro-6-(1′-tosylpyrrol-2′-yl)pyran-2-one (1)**

A mixture of *N*-tosylpyrrole (2.2 g, 10.0 mmol), glutaric acid (2.6 g, 20.0 mmol), and TFAA (16.8 g, 80.0 mmol) in anhyd $CH_2Cl_2$ (40 mL) was heated to reflux for 40 h and cooled. $H_2O$ (50 mL) was added to quench the reaction. The separated organic layer was washed successively with $H_2O$ (30 mL), sat. aq $NaHCO_3$ (30 mL) and $H_2O$ (30 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was purified by column chromatography on silica gel using EtOAc–PE (1:10, then 1: 3) as eluent to give dihydropyrone **1** (1.1 g, 35%) as a pale yellow solid; mp 134–137 °C.

IR (KBr): 1764, 1370, 1169, 1145, 1048 cm$^{-1}$.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 2.38 (3 H, s, $CH_3$), 2.42 (2 H, td, *J* = 7.4, 4.6 Hz, 4-$CH_2$), 2.65 (2 H, t, *J* = 7.4 Hz, 3-$CH_2$), 5.55 (1



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H, t, $J$ = 4.6 Hz, 5-H), 6.35 (1 H, t, $J$ = 3.3 Hz, 4′-H), 6.45 (1 H, dd, $J$ = 3.3, 1.8 Hz, 3′-H), 7.44 (2 H, d, $J$ = 8.4 Hz, ArH), 7.54 (1 H, dd, $J$ = 3.3, 1.8 Hz, 5′-H), 7.85 (2 H, d, $J$ = 8.4 Hz, ArH).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 18.5, 21.1, 27.5, 108.8, 112.4, 117.4, 124.7, 127.2, 127.3, 130.0, 135.1, 142.6, 145.5, 168.3.

MS (ESI): $m/z$ (%) = 340 (100, $[M^+ + Na]^+$), 318 (55, $[M + H]^+$).

HRMS-ESI: $m/z$ $[M + Na]^+$ calcd for $C_{16}H_{15}NO_4S$ + Na: 340.0619; found: 340.0626.

**5-Oxo-5-(1′-tosylpyrrol-2′-yl)pentanamide (2a)**

A mixture of dihydropyranone **1** (0.79 g, 2.5 mmol), $NH_4OAc$ (1.93 g, 25.0 mmol), and EtOH (15 mL) was heated to reflux for 3 h and then evaporated in vacuo. The residue was partitioned between $CH_2Cl_2$ (30 mL) and $H_2O$ (50 mL). The separated organic layer was dried ($Na_2SO_4$), filtered, and evaporated in vacuo. The residue was purified by column chromatography on silica gel using EtOAc–PE (5:1) as eluent to give keto amide **2a** (0.82 g, 98%) as a colorless solid; mp 71–73 °C.

IR (KBr): 3495, 3392, 1661, 1610, 1435, 1368, 1178, 1145, 1067 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.86 (2 H, quint, $J$ = 7.2 Hz, 3-$CH_2$), 2.15 (2 H, t, $J$ = 7.2 Hz, 2-$CH_2$), 2.36 (3 H, s, $CH_3$), 2.71 (2 H, t, $J$ = 7.2 Hz, 4-$CH_2$), 6.01 (1 H, br s, NH), 6.10 (1 H, br s, NH), 6.28 (1 H, t, $J$ = 3.5 Hz, 4′-H), 7.04 (1 H, dd, $J$ = 3.8, 1.7 Hz, 3′-H), 7.26 (2 H, d, $J$ = 8.4 Hz, ArH), 7.73 (1 H, dd, $J$ = 3.1, 1.7 Hz, 5′-H), 7.84 (2 H, d, $J$ = 8.4 Hz, ArH).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 20.3, 21.5, 34.2, 37.9, 110.3, 123.7, 128.0, 129.2, 130.0, 132.8, 135.5, 144.7, 175.2, 188.2.

MS (ESI): $m/z$ (%) = 357 (100, $[M + Na]^+$), 335 (18, $[M + H]^+$).

HRMS-ESI: $m/z$ $[M + Na]^+$ calcd for $C_{16}H_{18}N_2O_4S$ + Na: 357.0885; found: 357.0885.

***N*-Benzyl-5-oxo-5-(1′-tosylpyrrol-2′-yl)pentanamide (2b)**

A solution of dihydropyranone **1** (0.51 g, 1.6 mmol) and benzylamine (1.36 g, 12.7) in anhyd toluene (20 mL) was heated to reflux for 1 h. The cooled solution was washed with aq 1 M HCl (20 mL) and brine (20 mL), then dried ($Na_2SO_4$), filtered, and evaporated in vacuo to give keto amide **2b** (0.59 g, 88%) as a sticky oil.

IR (film): 3513, 1665, 1636, 1440, 1367, 1174, 1147, 1070 cm$^{-1}$.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 1.71 (2 H, quint, $J$ = 7.4 Hz, 3-$CH_2$), 2.12 (2 H, t, $J$ = 7.4 Hz, 2-$CH_2$), 2.38 (3 H, s, $CH_3$), 2.74 (2 H, t, $J$ = 7.4 Hz, 4-$CH_2$), 4.24 (2 H, d, $J$ = 5.8 Hz, C$H_2$Ph), 6.48 (1 H, t, $J$ = 3.4 Hz, 4′-H), 7.22–7.30 (6 H, m, ArH), 7.43 (2 H, d, $J$ = 8.1 Hz, ArH), 7.86–7.89 (3 H, m, ArH), 8.31 (1 H, t, $J$ = 5.8 Hz, NH).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 20.4, 21.1, 34.2, 38.0, 42.0, 111.0, 124.2, 126.7, 127.2, 127.9, 128.3, 129.6, 130.4, 132.9, 135.5, 139.5, 139.7, 144.9, 171.6, 188.2.

MS (ESI): $m/z$ (%) = 447 (26, $[M + Na]^+$), 425 (100, $[M + H]^+$).

HRMS-ESI: $m/z$ $[M + Na]^+$ calcd for $C_{23}H_{24}N_2O_4S$ + Na: 447.1354; found: 447.1374.

**3,4-Dihydro-6-(1′-tosylpyrrol-2′-yl)pyridinone (3a)**

A solution of keto amide **2a** (0.82 g, 2.45 mmol) and PTSA (0.25 g, 1.47 mmol) in toluene (20 mL) was heated to reflux using a Dean–Stark apparatus for 1 h and cooled. The solution was washed with $H_2O$ (30 mL), then dried ($Na_2SO_4$), filtered, and evaporated in vacuo. The residue was purified by column chromatography on silica gel using EtOAc–PE (1:1) as eluent to give dihydropyridinone **3a** (0.65 g, 84%) as a colorless solid; mp 130–132 °C.

IR (KBr): 3173, 1671, 1367, 1167, 1152, 1088, 1052 cm$^{-1}$.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 2.25–2.33 (4 H, m, 3- and 4-$CH_2$), 2.37 (3 H, s, $CH_3$), 4.81 (1 H, t, $J$ = 4.6 Hz, 5-H), 6.27–6.32 (2 H, m, 3′ and 4′-H), 7.39–7.44 (3 H, m, ArH), 7.69 (2 H, d, $J$ = 8.3 Hz, ArH), 9.23 (1 H, s, NH).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 20.1, 21.1, 29.9, 107.4, 112.6, 116.6, 124.3, 126.9, 129.6, 129.9, 130.0, 135.2, 145.2, 169.6.

MS (ESI): $m/z$ (%) = 339 (40, $[M + Na]^+$), 317 (100, $[M + H]^+$).

HRMS-ESI: $m/z$ $[M + H]^+$ calcd for $C_{16}H_{17}N_2O_3S$: 317.0960; found: 317.0949.

**1-Benzyl-3,4-dihydro-6-(1′-tosylpyrrol-2′-yl)pyridinone (3b)**

A solution of keto amide **2b** (0.80 g, 1.88 mmol) and PTSA (0.19 g, 1.13 mmol) in toluene (25 mL) was heated to reflux using a Dean–Stark apparatus for 24 h and cooled. The solution was washed with $H_2O$ (30 mL), then dried ($Na_2SO_4$), filtered, and evaporated in vacuo. The residue was purified by column chromatography on silica gel using EtOAc–PE (1:3) as eluent to give dihydropyridinone **3b** (0.68 g, 90%) as a colorless solid; mp 124–126 °C.

IR (KBr): 1679, 1385, 1365, 1173, 1152, 1087, 1052 cm$^{-1}$.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 2.32 (2 H, br, 4-$H_2$), 2.39 (3 H, s, $CH_3$), 2.60 (2 H, br, 3-$CH_2$), 3.55 (1 H, br, C*H*HPh), 5.06 (1 H, t, $J$ = 4.8 Hz, 5-H), 5.07 (1 H, br, CH*H*Ph), 5.89 (1 H, dd, $J$ = 3.3, 1.7 Hz, 3′-H), 6.25 (1 H, t, $J$ = 3.3 Hz, 4′ -H), 6.95 (2 H, d, $J$ = 6.8 Hz, ArH), 7.17–7.23 (3 H, m, ArH), 7.44 (2 H, d, $J$ = 8.3 Hz, ArH), 7.51 (1 H, dd, $J$ = 3.3, 1.7 Hz, 5′-H), 7.73 (2 H, d, $J$ = 8.3 Hz, ArH).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 19.2, 21.1, 30.8, 45.2, 112.7, 113.7, 118.1, 124.4, 126.1, 126.7, 126.9, 128.2, 130.0, 132.5, 134.9, 138.4, 145.5, 169.4.

MS (ESI): $m/z$ (%) = 429 (100, $[M + Na]^+$), 407 (75, $[M + H]^+$).

HRMS-ESI: $m/z$ $[M + Na]^+$ calcd for $C_{23}H_{22}N_2O_3S$ + Na: 429.1249; found: 429.1240.

**2-Bromo-6-(1′-tosylpyrrol-2′-yl)pyridine (4)**

*From **3a***: A solution of dihydropyridinone **3a** (50 mg, 0.16 mmol) and $POBr_3$ (900 mg, 3.14 mmol) in anhyd toluene (20 mL) was heated to reflux for 1.5 h, then cooled and diluted with EtOAc (50 mL). Ice-water was added carefully until no more bubbling was observed. The separated organic phase was washed successively with $H_2O$ (30 mL), sat. aq $NaHCO_3$ (20 mL) and brine (20 mL), then dried ($Na_2SO_4$), filtered, and evaporated in vacuo. The residue was purified by column chromatography on silica gel using EtOAc–PE (1:10) as eluent to give bromopyridine **4** (21 mg, 35%) as a colorless solid; mp 135–138 °C.

IR (KBr): 1583, 1545, 1422, 1371, 1170, 1145 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 2.41 (3 H, s, $CH_3$), 6.32 (1 H, t, $J$ = 3.3 Hz, 4′-H), 6.45 (1 H, dd, $J$ = 3.6, 1.7 Hz, 3′-H), 7.29 (2 H, d, $J$ = 8.2 Hz, ArH), 7.41 (1 H, dd, $J$ = 7.5, 0.9 Hz, ArH), 7.47–7.59 (3 H, m, ArH), 7.76 (2 H, d, $J$ = 8.2 Hz, ArH).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 21.7, 111.9, 117.5, 123.7, 125.4, 126.9, 127.8, 128.7, 129.7, 136.0, 138.3, 140.6, 145.0, 151.6.

MS (ESI): $m/z$ (%) = 401 (100, [M ($^{81}$Br) + Na]$^+$), 399 (100, [M ($^{79}$Br) + Na]$^+$), 379 (55, [M ($^{81}$Br) + H]$^+$), 377 (55, [M ($^{79}$Br) + H]$^+$).

HRMS-ESI: $m/z$ $[M + Na]^+$ calcd for $C_{16}H_{13}{}^{79}BrN_2O_2S$ + Na: 398.9779; found: 398.9773.

*From **3b***: Similarly, the title compound could also be synthesized in 65% isolated yield by refluxing a mixture of dihydropyridinone **3b** and $POBr_3$ in anhyd toluene for 5–8 h.

**2-Bromo-6-(1′-pyrrol-2′-yl)pyridine (8)**

A mixture of tosylpyrrolylpyridine **4** (80 mg, 0.21 mmol), NaOH (252 mg, 6.30 mmol), and MeOH (25 mL) was heated to reflux for 3.5 h and cooled. The bulk of the solvent was evaporated in vacuo.



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The residue was partitioned between EtOAc (30 mL) and $H_2O$ (30 mL). The separated organic layer was dried ($Na_2SO_4$), filtered, and evaporated in vacuo. The residue was purified by column chromatography on silica gel using EtOAc–PE (1:10) as eluent to give pyrrolylpyridine **8** (30 mg, 63%) as a colorless solid; mp 71–73 °C.

IR (KBr): 3380, 1585, 1542, 1437, 1159, 1118, 1101, 1034 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 6.20 (1 H, m, 4′-H), 6.63 (1 H, m, 3′-H), 6.82 (1 H, m, 5′-H), 7.10 (1 H, t, *J* = 4.2 Hz, 4-H), 7.35 (2 H, d, *J* = 4.2 Hz, 3- and 5-H), 9.45 (1 H, br s, NH).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 108.7, 110.7, 116.7, 121.0, 124.1, 129.6, 138.9, 140.9, 151.4.

MS (ESI): *m/z* (%) = 225 (100, [M ($^{81}Br$) + H]$^+$), 223 (100, [M ($^{79}Br$) + H]$^+$).

HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_9H_8{}^{79}BrN_2$: 222.9871; found: 222.9865.

**Suzuki Cross-Coupling Reaction; General Procedure**

A mixture of bromopyridine **4** (100 mg, 0.27 mmol), arylboronic acid (0.33 mmol), $Pd(PPh_3)_4$ (12 mg, 0.01 mmol), and $K_2CO_3$ (91 mg, 0.66 mmol) in toluene (25 mL)–MeOH (5 mL) was heated to reflux under $N_2$. The reaction was monitored by TLC. Upon completion of the reaction (reaction time as indicated below), the bulk of the solvents were removed in vacuo. The residue was partitioned between EtOAc (30 mL) and $H_2O$ (20 mL). The separated organic layer was dried ($Na_2SO_4$), then evaporated in vacuo. The crude product was purified by column chromatography.

**2-Phenyl-6-(1′-pyrrol-2′-yl)pyridine (6a)**

*From **4***: The reaction mixture was heated to reflux for 15 h. The crude product was purified by column chromatography on silica gel using EtOAc–PE (1:10) as eluent to give pyrrolylpyridine **6a** (98%) as a colorless solid; mp 96–101 °C.

IR (KBr): 3399, 1592, 1568, 1457, 1116, 1102, 1083, 1035 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 6.33 (1 H, m, 4′-H), 6.75 (1 H, m, 3′-H), 6.94 (1 H, m, 5′-H), 7.43–7.52 (5 H, m, ArH), 7.70 (1 H, t, *J* = 7.8 Hz, 4-H), 8.30–8.06 (2 H, m, 3- and 5-H), 9.72 (1 H, br s, NH).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 107.2, 110.2, 116.5, 117.3, 119.7, 126.9, 128.6, 128.9, 131.6, 137.2, 139.4, 150.1, 156.3.

MS (ESI): *m/z* (%) = 243 (11, [M + Na]$^+$), 221 (100, [M + H]$^+$).

HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{15}H_{13}N_2$: 221.1079; found: 221.1079.

*From **8***: The title compound could also be synthesized in 89% isolated yield by refluxing a mixture of bromide **8** (50 mg, 0.22 mmol), phenylboronic acid (34 mg, 0.28 mmol), $Pd(PPh_3)_4$ (cat. amount), and $K_2CO_3$ (77 mg, 0.56 mmol) in toluene (20 mL)–MeOH (5 mL) for 20 h.

**2-(4′-Fluorophenyl)-6-(1″-pyrrol-2″-yl)pyridine (6b)**

The reaction mixture was heated to reflux for 23 h. The crude product was purified by column chromatography on silica gel using EtOAc–PE (1:10) as eluent to give pyrrolylpyridine **6b** (92%) as a colorless solid; mp 97–99 °C.

IR (KBr): 3397, 1601, 1566, 1510, 1456, 1230, 1164, 1106 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 6.33 (1 H, m, 4′-H), 6.77 (1 H, m, 3′-H), 6.95 (1 H, m, 5′-H), 7.17 (2 H, t, *J* = 8.6 Hz, 3′- and 5′-H), 7.43 (1 H, d, *J* = 7.8 Hz, ArH), 7.49 (1 H, d, *J* = 7.8 Hz, ArH), 7.69 (1 H, t, *J* = 7.8 Hz, 4-H), 8.03 (2 H, dd, *J* = 8.6, 5.5 Hz, 2′- and 6′-H), 9.70 (1 H, br s, NH).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 107.4, 110.3, 115.5 (d, $J_{F,C}$ = 21.5 Hz), 116.4, 116.9, 119.8, 128.7 (d, $J_{F,C}$ = 8.3 Hz), 133.5 (d, $J_{F,C}$ = 302.9 Hz), 137.3, 150.2, 155.3, 161.8, 165.1.

MS (ESI): *m/z* (%) = 261 (11, [M + Na]$^+$), 239 (100, [M + H]$^+$).

HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{15}H_{12}FN_2$: 239.0985; found: 239.0983.

**2-(4′-Methoxyphenyl)-6-(1″-tosylpyrrol-2″-yl)pyridine (5c) and 2-(4′-Methoxyphenyl)-6-(1″-pyrrol-2″-yl)pyridine (6c)**

*Formation of **5c***: The reaction mixture was heated to reflux for 12 h. The crude product was purified by column chromatography on silica gel using EtOAc–PE (1:10) as eluent to give tosylpyrrolylpyridine **5c** (81%) as a colorless solid; mp 128–132 °C.

IR (KBr): 1610, 1590, 1572, 1514, 1438, 1371, 1296, 1253, 1171, 1146, 1089, 1063, 1028 $cm^{-1}$.

$^1H$ NMR (300 MHz, DMSO-$d_6$): δ = 2.33 (3 H, s, $CH_3$), 3.87 (3 H, s, $CH_3O$), 6.35 (1 H, t, *J* = 3.3 Hz, 4″-H), 6.46 (1 H, dd, *J* = 3.3, 1.8 Hz, 3″-H), 6.92 (2 H, d, *J* = 8.4 Hz, ArH), 7.07 (2 H, d, *J* = 8.0 Hz, ArH), 7.36 (1 H, d, *J* = 7.5 Hz, ArH), 7.45 (1 H, dd, *J* = 3.3, 1.8 Hz, 5″-H), 7.51 (2 H, d, *J* = 8.0 Hz, ArH), 7.60 (1 H, d, *J* = 7.8 Hz, ArH), 7.62–7.77 (3 H, m, ArH).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 21.6, 55.4, 111.9, 113.8, 116.8, 119.0, 123.3, 124.8, 127.2, 128.7, 129.5, 131.3, 136.3, 136.7, 144.4, 150.3, 156.0, 160.5.

MS (ESI): *m/z* (%) = 427 (41, [M + Na]$^+$), 405 (100, [M + H]$^+$), 357 (15).

HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{23}H_{21}N_2O_3S$: 405.1273; found: 405.1265.

*Formation of **6c***: The reaction mixture was heated to reflux for 35 h. The crude product was purified by column chromatography on silica gel using EtOAc–PE (1:10) as eluent to give pyrrolylpyridine **6c** (71%) as a colorless solid; mp 150–155 °C.

IR (KBr): 3410, 1607, 1591, 1564, 1515, 1457, 1299, 1249, 1182, 1111, 1037, 1025 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 3.87 (3 H, s, $CH_3$), 6.32 (1 H, m, 4″-H), 6.73 (1 H, m, 3″-H), 6.93 (1 H, m, 5″-H), 7.01 (2 H, d, *J* = 9.0 Hz, 3′- and 5′-H), 7.40–7.44 (2 H, m, 3- and 5-H), 7.65 (1 H, t, *J* = 7.8 Hz, 4-H), 8.01 (2 H, d, *J* = 9.0 Hz, 2′- and 6′-H), 9.70 (1 H, br s, NH).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 55.4, 107.1, 110.3, 114.0, 115.9, 116.6, 119.6, 128.2, 128.5, 131.6, 137.3, 149.9, 155.8, 160.5.

MS (ESI): *m/z* (%) = 273 (9, [M + Na]$^+$), 251 (100, [M + H]$^+$).

HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{16}H_{15}N_2O$: 251.1184; found: 251.1172.

**2-(4′-*tert*-Butylphenyl)-6-(1″-tosylpyrrol-2″-yl)pyridine (5d) and 2-(4′-*tert*-Butylphenyl)-6-(1″-pyrrol-2″-yl)pyridine (6d)**

The reaction mixture was heated to reflux for 11 h. The crude product was purified by column chromatography on silica gel using EtOAc–PE (1:10) as eluent to give tosylpyrrolylpyridine **5d** (66%) and pyrrolylpyridine **6d** (27%) both as colorless solids; mp 153–156 °C.

**5d**

IR (KBr): 1591, 1573, 1441, 1360, 1170, 1149, 1088 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 1.38 [9 H, s, $C(CH_3)_3$], 2.32 (3 H, s, $CH_3$), 6.36 (1 H, t, *J* = 3.2 Hz, 4″-H), 6.48 (1 H, m, 3″-H), 7.05 (2 H, d, *J* = 8.1 Hz, ArH), 7.41–7.78 (10 H, m ArH).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 21.6, 31.3, 34.6, 111.9, 116.5, 119.4, 123.5, 124.7, 125.4, 127.0, 127.2, 129.5, 136.2, 136.3, 136.5, 144.3, 150.5, 151.9, 156.5.

MS (ESI): *m/z* (%) = 453 (41, [M + Na]$^+$), 431 (100, [M + H]$^+$).

HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{26}H_{27}N_2O_2S$: 431.1793; found: 431.1771.



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**6d**
Mp 109–110 °C.

IR (KBr): 3451, 1593, 1566, 1458, 1092, 1079 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 1.38 [9 H, s, $C(CH_3)_3$], 6.32 (1 H, m, 4″-H), 6.74 (1 H, m, 3″-H), 6.93 (1 H, m, 5″-H), 7.46 (2 H, d, *J* = 7.8 Hz, 3- and 5-H), 7.51 (2 H, d, *J* = 8.4 Hz, 3′- and 5′-H), 7.67 (1 H, t, *J* = 7.8 Hz, 4-H), 7.97 (2 H, d, *J* = 8.4 Hz, 2′- and 6′-H), 9.71 (1 H, br s, NH).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 31.3, 34.7, 107.0, 110.3, 116.2, 117.2, 119.5, 125.6, 126.6, 131.8, 137.2, 150.0, 152.1, 156.3.

MS (ESI): *m*/*z* (%) = 299 (13, $[M + Na]^+$), 277 (100, $[M + H]^+$).

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{21}N_2$: 277.1705; found: 277.1700.

**2-(2′-Methylphenyl)-6-(1″-tosylpyrrol-2″-yl)pyridine (5e) and 2-(2′-Methylphenyl)-6-(1″-pyrrol-2″-yl)pyridine (6e)**
The reaction mixture was heated to reflux for 11 h. The crude product was purified by column chromatography on silica gel using EtOAc–PE (1:5) as eluent to give tosylpyrrolylpyridine **5e** (44%) as a colorless solid and pyrrolylpyridine **6e** (49%) as an orange oil.

**5e**
Mp 111–113 °C.

IR (KBr): 1572, 1447, 1360, 1170, 1145, 1083, 1060 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 2.08 (3 H, s, $CH_3$), 2.18 (3 H, s, $CH_3$), 6.25 (1 H, t, *J* = 3.6 Hz, 4″-H), 6.41 (1 H, dd, *J* = 3.3, 1.8 Hz, 3″-H), 6.80 (2 H, d, *J* = 8.1 Hz, ArH), 7.14–7.24 (5 H, m, ArH), 7.38–7.42 (4 H, m, ArH), 7.65 (1 H, t, *J* = 7.8 Hz, 4-H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 20.2, 21.5, 111.8, 116.9, 122.8, 125.2, 125.7, 127.2, 128.2, 129.2, 129.6, 130.3, 135.0, 136.2, 136.3, 140.0, 144.1, 149.9, 158.8.

MS (ESI): *m*/*z* (%) = 411 (39, $[M + Na]^+$), 389 (100, $[M + H]^+$).

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{21}N_2O_2S$: 389.1324; found: 389.1311.

**6e**
IR (film): 3424, 1589, 1567, 1458, 1160, 1103, 1031 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 2.30 (3 H, s, $CH_3$), 6.20 (1 H, m, 4″-H), 6.64 (1 H, m, 3″-H), 6.76 (1 H, m, 5″-H), 7.02 (1 H, d, *J* = 7.8 Hz, ArH), 7.17–7.22 (3 H, m, ArH), 7.34 (1 H, m, ArH), 7.38 (1 H, d, *J* = 7.8 Hz, ArH), 7.56 (1 H, t, *J* = 7.8 Hz, 4-H), 9.53 (1 H, br s, NH).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 20.5, 107.1, 110.2, 116.0, 119.7, 120.7, 125.8, 128.3, 129.5, 130.7, 131.5, 135.9, 136.8, 140.4, 149.6, 158.9.

MS (ESI): *m*/*z* (%) = 257 (10, $[M + Na]^+$), 235 (100, $[M + H]^+$).

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{15}N_2$: 235.1235; found: 235.1229.

**2-(3′-Nitrophenyl)-6-(1″-tosylpyrrol-2″-yl)pyridine (5f) and 2-(3′-Nitrophenyl)-6-(1″-pyrrol-2″-yl)pyridine (6f)**
The reaction mixture was heated to reflux for 13 h. The crude product was purified by column chromatography on silica gel using EtOAc–PE (1:5) as eluent to give tosylpyrrolylpyridine **5f** (57%) as a colorless solid and pyrrolylpyridine **6f** (32%) as an amorphous solid.

**5f**
Mp 159–162 °C.

IR (KBr): 1590, 1528, 1371, 1351, 1170 1146, 1080 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 2.31 (3 H, s, $CH_3$), 6.39 (1 H, t, *J* = 3.3 Hz, 4″-H), 6.51 (1 H, dd, *J* = 3.3, 1.5 Hz, 3″-H), 7.07 (2 H, d, *J* = 8.1 Hz, ArH), 7.47–7.55 (4 H, m, ArH), 7.59 (1 H, t, *J* = 8.1 Hz, 4-H), 7.73 (1 H, dd, *J* = 8.1, 0.7 Hz, ArH), 7.84 (1 H, t, *J* = 7.8 Hz, 5′-H), 8.15–8.25 (2 H, m, 4′- and 6′-H), 8.65 (1 H, t, *J* = 1.8 Hz, 2′-H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 21.5, 112.1, 116.9, 119.6, 122.1, 123.4, 124.9, 125.1, 127.0, 129.5, 133.0, 134.9, 136.3, 137.0, 140.8, 144.7, 148.6, 151.2, 153.8.

MS (ESI): *m*/*z* (%) = 442 (70, $[M + Na]^+$), 420 (100, $[M + H]^+$).

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{18}N_3O_4S$: 420.1018; found: 420.0992.

**6f**
IR (KBr): 3434, 1594, 1566, 1524, 1455, 1344, 1274, 1170, 1103, 1040 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 6.26 (1 H, m, 4″-H), 6.70 (1 H, m, 3″-H), 6.90 (1 H, m, 5″-H), 7.45 (1 H, d, *J* = 7.8 Hz, ArH), 7.47 (1 H, d, *J* = 7.8 Hz, ArH), 7.56 (1 H, t, *J* = 8.1 Hz, 5′-H), 7.66 (1 H, t, *J* = 7.8 Hz, 4-H), 8.16–8.29 (2 H, m, 4′- and 6′-H), 8.83 (1 H, t, *J* = 2.1 Hz, 2′-H), 9.62 (1 H, br s, NH).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 108.2, 110.6, 117.4, 117.8, 120.5, 121.9, 123.6, 129.6, 130.9, 132.7, 137.8, 140.8, 148.8, 150.5, 153.5.

MS (ESI): *m*/*z* (%) = 288 (71, $[M + Na]^+$), 266 (100, $[M + H]^+$).

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{12}N_3O_2$: 266.0930; found: 266.0957.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are $^1H$ and $^{13}C$ NMR spectra for all new compounds

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