# Coupling of Arylboronic Acids with a Partially Reduced Pyridine Derivative

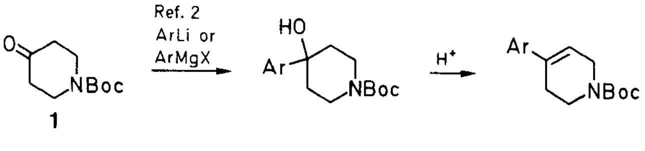
David J. Wustrow,* Lawrence D. Wise

Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, 2800 Plymouth Rd., Ann Arbor, MI 48106-1047, USA

*tert*-Butylcarbonyl 1,2,3,6-tetrahydro-4-[(trifluoromethyl)sulfonyloxy]pyridine-1-carboxylate (**2**) was prepared and underwent palladium-catalyzed coupling reactions with a variety of substituted arylboronic acids **3** to produce a series of *tert*-butyl-4-aryl-1,2,3,6-tetrahydropyridine-1-carboxylates **4**.

4-Aryltetrahydropyridines continue to be of interest in part because of their wide range of biological activities. These include interactions with dopaminergic,[1] adrenergic[2] and sigma[3] receptors. The study of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and related compounds with regard to their toxicity to cells found in the substantia nigra and their relevance to Parkinson's disease has also contributed greatly to interest in the preparation of 4-aryltetrahydropyridines.[4] As part of our ongoing program to synthesize novel dopamine autoreceptor agonists, we desired a convenient way to access a variety of 1-*tert*-butoxycarbonyl (Boc) protected 4-aryltetrahydropyridines **4** which could be easily purified and then deprotected.

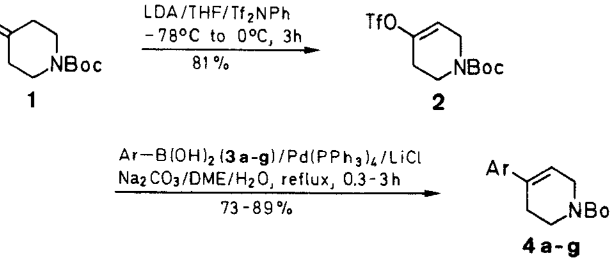
*N*-Boc protected tetrahydropyridines can be prepared in low yield by direct condensation of aryllithium or aryl Grignard reagents with protected 4-piperidinone **1**,[2] followed by elimination of the resulting alcohol (Scheme **1**). Competing attack by the arylmetal species on the Boc group resulted in low yields of the intermediate alcohols. In addition, poor yields were obtained from the dehydration reaction.[5]



Scheme 1

A direct coupling reaction between a tetrahydropyridine derivative and a suitable aryl intermediate was needed to circumvent both problems. Arylboronic acids have been shown to undergo a mild palladium-catalyzed cross coupling reaction with aryl halides[6] and heteroaryl halides.[7] In these reactions the boronic acids have been shown to be synthetic equivalents for arylmetal species which can be conveniently prepared and stored. Recently, palladium-catalyzed coupling of boronate species with both aryl triflates and the enol triflate of 4-*tert*-butylcyclohexanone has been reported.[8,9] Application of this methodology to heterocyclic enol triflates has to our knowledge not been examined. Herein we describe the preparation of tetrahydropyridinyl triflate **2** and its successful reaction with a series of substituted phenylboronic acids to prepare a variety of aryltetrahydropyridines.

Triflate **2** was conveniently prepared by deprotonation of the piperidinone derivative **1** and quenching the resulting enolate with *N*-phenyltrifluoromethanesulfonimide (Scheme **2**).[10] Other workers have commented on the difficulty of separating enol triflates from the *N*-phenyltrifluoromethanesulfonamide byproduct produced in this reaction,[11] however we have found that vinyl triflate **2** could be easily purified by passing the



| 3,4 | Ar | 3,4 | Ar |
|---|---|---|---|
| **a** | 4-$ClC_6H_4$ | **e** | 2,4-$Cl_2C_6H_3$ |
| **b** | 4-$MeOC_6H_4$ | **f** | 3-$NO_2C_6H_4$ |
| **c** | 4-$FC_6H_4$ | **g** | 1-naphthyl |
| **d** | 4-$MeC_6H_4$ | | |

Scheme 2

**Table 1.** 4-Aryl-1,2,3,6-tetrahydropyridine-1-carboxylates

| Product | Time (min) | Yield (%)[a] | Molecular Formula[b] | IR (KBr) $\nu$ ($cm^{-1}$) | MS (70 eV) $m/z$ (%) | $^1H$-NMR ($CDCl_3$/TMS) $\delta$, $J$ (Hz) |
|---|---|---|---|---|---|---|
| **4a** | 20 | 83 | $C_{16}H_{20}ClNO_2$ (293.8) | 2978, 1694, 1410, 1169, 1093 | 293 ($M^+$, 2), 236 (100) | 1.49 (s, 9H), 2.49 (m, 2H), 3.63 (t, 2H, $J = 6$), 4.09 (d, 2H, $J = 1$), 6.01 (m, 1H), 7.28 (m, 4H) |
| **4b** | 20 | 73 | $C_{17}H_{23}NO_3$ (289.4) | 2952, 1694, 1410, 1169, 1093 | 232 (M-*t*-Bu, 100), 216 (8) | 1.49 (s, 9H), 2.49 (m, 2H), 3.62 (t, 2H, $J = 6$), 3.81 (s, 3H), 4.05 (d, 2H, $J = 3$), 5.93 (m, 1H), 6.86 (d, 2H, $J = 9$), 7.31 (d, 2H, $J = 9$) |
| **4c** | 90 | 84 | $C_{16}H_{20}FNO_2$ (277.3) | 2979, 1693, 1433, 1234 | 277 ($M^+$, 4), 220 (100) | 1.42 (s, 9H), 2.43 (m, 2H), 3.53 (t, 2H, $J = 6$), 3.98 (d, 2H, $J = 2$), 6.10 (m, 1H), 7.16 (t, 2H, $J = 8$), 7.45 (dd, 2H, $J = 8, 3$) |
| **4d** | 180 | 75 | $C_{17}H_{23}NO_2$ (274.4) | 2985, 1695, 1412, 1145 | 273 ($M^+$, 2), 216 (100) | 1.50 (s, 9H), 2.35 (s, 3H), 3.52 (m, 2H), 3.64 (t, 2H, $J = 6$), 4.07 (d, 2H, $J = 2$), 6.02 (m, 1H), 7.16 (d, 2H, $J = 8$), 7.29 (d, 2H, $J = 8$) |
| **4e** | 120 | 85 | $C_{16}H_{19}Cl_2NO_2$ (328.2) | 2987, 1691, 1410, 1090 | 327 ($M^+$, 3), 270 (100) | [d]1.43 (s, 9H), 2.34 (m, 2H), 3.53 (t, 2H, $J = 6$), 3.96 (d, 2H, $J = 2$), 5.74 (m, 1H), 7.31 d, 1H, $J = 8$), 7.42 (dd, 1H, $J = 8, 2$), 7.62 (d, 1H, $J = 2$) |
| **4f** | 180 | 83 | $C_{16}H_{20}N_2O_4$ (304.4) | 2986, 1693, 1520, 1345 | 247 (M-*t*-Bu, 100) | 1.50 (s, 9H), 2.55 (m, 2H), 3.67 (t, 2H, $J = 6$), 4.12 (m, 2H), 6.20 (m, 1H), 7.51 (t, 1H, $J = 6$), 7.69 (d, 1H, $J = 8$), 8.11 (d, 1H, $J = 8$), 8.23 (s, 1H) |
| **4g** | 120 | 89 | $C_{20}H_{23}NO_2$ (309.4) | 2985, 1685, 1448, 1115 | [c]308 ($M^+$, 31), 252 (100) | 1.53 (s, 9H), 2.50 (m, 2H), 3.71 (t, 2H, $J = 6$), 4.12 (d, 2H, $J = 1$), 5.74 (m, 1H), 7.24 (dd, 1H, $J = 8, 1$), 7.39 (d, 1H, $J = 8$), 7.44 (m, 2H), 7.73 (d, 1H, $J = 8$), 7.83 (m, 1H), 7.93 (m, 1H) |

[a] After isolation via silica gel chromatography.

[b] Satisfactory FAB-HRMS obtained M-H +/− 0.0014 amu.

[c] FAB-MS.

[d] Spectrum obtained in DMSO-$d_6$.

**Table 2.** $^{13}C$-Spectra of Selected Compounds

| Product | $^{13}C$-NMR ($CDCl_3$/TMS), $\delta$, $J$ (Hz) |
|---|---|
| **2** | 28.06, 28.32, 40.40, 41.67, 80.59, 115.92, 121.01, 146.89, 154.31 |
| **4a** | 27.34, 28.50, 43.67, 79.77, 121.39, 126.19, 128.53, 128.50, 132.93, 134.28, 139.08, 154.80 |
| **4b** | 27.46, 28.52, 39.93, 43.68, 55.30, 79.16, 113.78, 119.13, 125.99, 133.30, 134.72, 154.88, 158.91 |
| **4c** | 27.52, 28.49, 39.95, 43.69, 79.79, 113.4, 115.21 (d, $J = 21$), 126.48 (d, $J = 8$ Hz), 127.08, 136.84, 154.90, 162.12 (d, $J = 250$) |
| **4d** | 21.08, 27.40, 28.51, 40.01, 43.66, 79.64, 124.78, 125.25, 129.11, 129.61, 136.01, 138.07, 154.87 |
| **4f** | 27.36, 28.50, 40.05, 43.71, 79.75, 119.84, 120.05, 121.97, 129.37, 130.82, 136.24, 143.32, 151.74, 154.91 |
| **4g** | 28.61, 30.99, 41.28, 43.62, 79.75, 123.92, 125.02, 124.47 (2C), 125.79, 125.94, 127.42, 128.47, 131.13, 133.82, 136.53, 141.01, 155.09 |

mixture through neutral alumina. Vinyl triflate **2** could also be stored for several months in the refrigerator without significant decomposition. Arylboronic acids are most easily prepared by reaction of an aryllithium or aryl Grignard species with a trialkyl borate and hydrolysis of the resulting borate ester.[7] Several substituted arylboronic acids are commercially available.

Reaction of enol triflate **2** with a variety of arylboronic acids **3** in the presence of base, lithium chloride and tetrakis(triphenylphosphine)palladium(0) proceeded smoothly to give the tetrahydropyridines **4a–g** (Scheme 2). The reaction was successful with a variety of arylboronic acids containing both electron-donating and electron-withdrawing substituents as well as **3e** which contains a substituent *ortho* to the boronic acid or the sterically hindered 1-napthylboronic acid (**3g**). Thus, the reaction does not appear to be extremely sensitive to electronic or steric effects of the boronic acids. Reactions were monitored by TLC and were typically complete within two hours. In favorable cases the reaction was complete within 20 minutes.

This method provides convenient access to 4-substituted tetrahydropyridines **4** from the readily available enol triflate **2** and arylboronic acids **3**. The application of this methodology demonstrates a useful alternative to aryl-olefin bond formation via condensation and elimination when such operations are precluded by other functionality in the molecule incompatible with harsh nucleophiles and elimination conditions. In addition, this chemistry should be applicable to analogs of enol triflate **2** which have amide or urea nitrogen protecting groups. Enol triflate **2** could serve as a versatile precursor for the introduction of partially reduced pyridine functionality into a variety of other substrates. This work is complementary to methodology employing cycloalkenyl and tetrahydropyridinyl tin reagents developed by others in these laboratories.[12]

IR spectra were recorded on a Nicolet MX-1 FT Spectrophotometer. $^1H$-NMR and $^{13}C$-NMR spectra were recorded on a Bruker AM250 or Varian XL300 NMR spectrometer. Electron impact mass spectra were recorded on a Finnegan 4500 or a VG Analytical 7070E/HF mass spectrometer. FAB and FAB high resolution mass spectra were run on a VG Analytical 7070E/HF using 1 mA of 7 KV Xenon target gas and PEG400 as the matrix. Boronic acids and

*N*-phenyltrifluoromethanesulfonimide were obtained from commercial sources (Aldrich or Lancaster Synthesis) and were used without further purification. Column chromatography was performed using E. Merck silica gel (230–400 mesh).

**_tert_-Butyl 1,2,3,6-Tetrahydro-4-[(trifluoromethyl)sulfonyloxy]-pyridine-1-carboxylate (2):**

A solution of *tert*-butyl 4-oxopiperidine-1-carboxylate[2] (**1**; 20.0 g, 100.4 mmol) in THF (100 mL) is added dropwise to a solution of lithium diisopropylamide (LDA, 110 mmol) in THF (100 mL) at −78 °C. After 20 min a solution of *N*-phenyltrifluoromethanesulfonimide (38.2 g, 107 mmol) in THF (100 mL) is added and the reaction is then warmed to 0 °C and allowed to stir for 3 h. The THF is removed under reduced pressure and the residue is dissolved in $CH_2Cl_2$ (45 mL) and loaded onto a pad of neutral alumina and eluted with hexane/EtOAc 9:1 to obtain compound **2** as an oil at r.t. which solidifies on standing in the refrigerator; yield: 26.9 g (81 %).

$^1$H-NMR ($CDCl_3$/TMS): $\delta = 1.48$ (s, 9H), 2.44 (t, 2H), 3.64 (t, 2H, $J$ = 6 Hz), 4.05 (dd, 2H, $J$ = 4,3 Hz), 5.77 (m, 1H).

FAB-HRMS: $m/z$, $C_{11}H_{16}F_3NO_5S$ calc.: 332.0780; found: 332.0780.

**_tert_-Butyl 1,2,3,6-Tetrahydro-4-(1-naphthyl)pyridine-1-carboxylate (4g); Typical Procedure:**

A three neck flask which has been purged with $N_2$ is charged with aq $Na_2CO_3$ (14.36 mL of a 2 M solution), 1,2-dimethoxyethane (DME, 35 mL), 1-napthylboronic acid (2.47 g, 14.36 mmol), LiCl (1.30 g, 30.78 mmol), vinyl triflate **2** (3.4 g, 10.26 mmol) and $Pd(PPh_3)_4$ (0.59 g, 0.513 mmol). The mixture is heated to reflux with vigorous stirring. After 2 h the reaction is cooled to r.t. and concentrated under reduced pressure. The residue is partitioned between $CH_2Cl_2$ (100 mL) and aq 2 N $Na_2CO_3$ (100 mL) and conc. $NH_4OH$ (6 mL). The aqueous layer is extracted again with $CH_2Cl_2$ (100 mL) and the combined organic extracts are dried ($Na_2SO_4$). The solvents are removed under reduced pressure and the residue is chromatographed on silica gel (hexane/EtOAc/$CH_2Cl_2$, 5:1:1) to obtain **4g** as a white solid; yield: 2.82 g (89 %): mp 82–83 °C (EtOAc/hexane).

| | | | | |
|---|---|---|---|---|
| $C_{20}H_{23}NO_2$ | calc. | C 77.64 | H 7.49 | N 4.53 |
| (309.4) | found | 77.42 | 7.48 | 4.57 |

*Spectral and analytical data was obtained through the Analytical Chemistry Department under the supervision of Gary McClusky. Thanks to Anne Giordani for high resolution mass spectra. Victor Snieckus (University of Waterloo) is acknowledged for a helpful discussion.*

Received: 1 April 1991; revised: 27 June 1991

(1) Seyfried, C.A.; Boettcher, H. *Drugs Future* **1990**, *15*, 819.
(2) Saari, W.S.; Halczenko, W.; Huff, J.R.; Guara, J.P.; Jr.; Hunt, C.A.; Randall, W.C.; Lotti, V.J.; Yarbough, G.G. *J. Med. Chem.* **1984**, *27*, 1182.
(3) Largent, B.L.; Wikstrom, H.; Gundlach, A.L.; Snyder, S.H. *Mol. Pharmacol.* **1988**, *32*, 772.
(4) Maret, G.; El Tayler, N.; Carrupt, P.A.; Testa, B.; Jenner, P.; and Baird, M. *Biochem. Pharmacol.* **1990**, *40*, 783.
Rollema, H.; Johnson, E.A.; Booth, R.G.; Caldera, P.; Lampen, P.; Youngster, S.K.; Trevor, A.J.; Naimen, N.; Castagnoli, N.Jr. *J. Med. Chem.* **1990**, *33*, 2221 and references cited there in.
(5) Kesten, S.R.; Johnson, S.J.; unpublished results from these laboratories, 1989.
(6) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513.
(7) Thompson, W.J.; Gaudino, J. *J. Org. Chem.* **1984**, *49*, 5237.
(8) For a review see: Terashima, M.; Ishikura, M. *Adv. Heterocycl. Chem.* **1989**, *46*, 143.
(9) Fu, J.-M.; Snieckus, V. *Tetrahedron Lett.* **1990**, *31*, 1665.
Oh-e, T.; Miyaura, N.; Suzuki, A. *Synlett* **1990**, 221.
(10) Mc Murry, J.E.; Scott, W.J. *Tetrahedron Lett.* **1983**, *24*, 979.
(11) Tius, M.A.; Kannangara, G.S.K. *J. Org. Chem.* **1990**, *55*, 5711.
(12) Laborde, E.; Lesheski, L.E.; Kiely, J.S.; *Tetrahedron Lett.* **1989**, *30*, 1837.
Laborde, E.; Kiely, J.S.; Lesheski, L.E.; Schroeder, M.C. *J. Heterocycl. Chem.* **1991**, *28*, 191.