

Supplementary Material

Rapid Microwave-Assisted Synthesis of N-Aryl 1,2,3,4-Tetrahydroisoquinolines

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1. General Information

1,2,3,4-Tetrahydroisoquinoline (95%), potassium *tert*-butoxide (reagent grade, 98%) and Cyclohexyl JohnPhos (97%) were purchased from Sigma-Aldrich. Palladium(II) acetate (99%) was purchased from Precious Metals Online. Dried toluene and *tert*-butanol were purchased from Merck. Analytical thin-layer chromatography (TLC) was performed on Merck Kieselgel 60F₂₅₄ aluminium backed plates and visualized using a 254 nm UV lamp and a combination of phosphomolybdic acid, ceric ammonium molybdate or potassium permanganate stain and heat. Flash chromatography was performed on silica gel (Merck Kieselgel 60, 0.040-0.063 mm) unless otherwise noted, according to the method of Still et al.¹ Infrared spectra were recorded neat on a Thermo Scientific Nicolet 6700 spectrometer in attenuated total reflectance (ATR) mode. Spectra were obtained between 4000 and 400 cm⁻¹ using 16 scans. NMR spectra were recorded on Bruker AV-400 instrument at 400.13 MHz for ¹H nuclei and at 100.61 MHz for ¹³C nuclei. Samples were recorded in deuterated chloroform and data acquired at 25 °C. Chemical shifts are reported as δ values in parts per million (ppm). In reporting spectral data the following abbreviations have been used: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High-resolution mass spectrometric analyses were performed on a Thermo Scientific Q Exactive mass spectrometer fitted with a HESI-II ion source. Positive and negative ions were recorded in an appropriate mass range at 140,000 mass resolution. The probe was used with 0.3 mL/min flow of solvent and the nitrogen nebulizing/desolvation gas used for vaporization was heated to 350 °C in these experiments. The sheath gas flow rate was set to 35 and the auxiliary gas flow rate to 25 (both arbitrary units). The spray voltage was 3.0 kV and the capillary temperature was 300 °C. Microwave reactions were performed using a Biotage Initiator robot.

2. Experimental Section

2.1 General procedure A: Microwave-assisted amination of aryl iodides

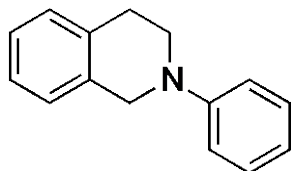
To a 2 mL Biotage microwave vial equipped with a stirbar was added Pd(OAc)₂ (5.6 mg, 5 mol%), CyJohnPhos (9.6 mg, 5.5 mol%), KO^t-Bu (78.4 mg, 1.4 equiv.) and aryl iodide (0.5 mmol, 1 equiv.) (if solid aryl iodide used). The vial was sealed with an aluminium crimp top cap fitted with a septum and purged with argon. *t*-BuOH (1.0 mL) was added via syringe, followed by aryl iodide (0.5 mmol, 1 equiv.) (if liquid aryl iodide used) and then 1,2,3,4-tetrahydroisoquinoline (75 μL, 1.2 equiv.). The vial was irradiated at 100 °C for 5 minutes then cooled to room temperature. The reaction mixture was diluted with EtOAc (10 mL), then filtered through Celite®. The resulting filtrate was washed with saturated NaCl solution, dried over MgSO₄ and concentrated under reduced pressure to yield the crude product.

2.2 General procedure B: Microwave-assisted amination of pyridyl bromides

The reaction was conducted as per general procedure A, except pyridyl bromides were employed instead of aryl iodides and microwave irradiation was performed for 30 minutes.

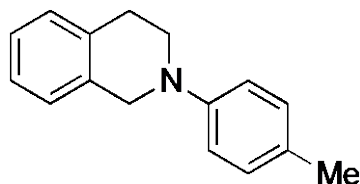
2.3 Compound characterisation data

2-Phenyl-1,2,3,4-tetrahydroisoquinoline (3a)



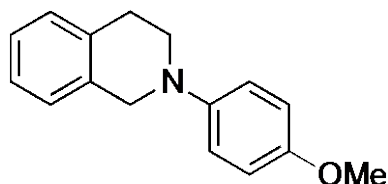
Iodobenzene (104.5 mg, 0.5 mmol) was treated according to general procedure A. Purification by flash chromatography (5:95 EtOAc/*n*-heptane) afforded the *title compound* **3** (100.4 mg, 96%), as a white solid. Spectroscopic data matched those previously reported in the literature.² δ_H 7.32-7.27 (m, 2H), 7.21-7.15 (m, 4H), 7.00 (dd, *J* = 8.8, 1.0 Hz, 2H), 6.84 (t, *J* = 7.3, 1.0 Hz, 1 H) 4.42 (s, 2H), 3.58 (t, *J* = 5.9 Hz, 2H), 3.00 (t, *J* = 5.9 Hz, 2H). δ_C 150.7, 135.0, 134.6, 129.3, 128.6, 126.7, 126.4, 126.1, 118.8, 115.3, 50.9, 46.6, 29.2.

2-(*p*-Tolyl)-1,2,3,4-tetrahydroisoquinoline (3b)



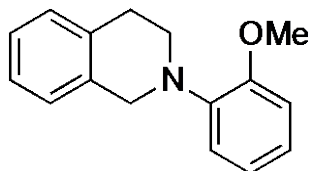
1-Iodo-4-methylbenzene (108.9 mg, 0.5 mmol) was treated according to general procedure A. Purification by flash chromatography (2.5:97.5 EtOAc/*n*-heptane) afforded the *title compound* **3b** (99.3 mg, 89%) as a white solid. Spectroscopic data matched those previously reported in the literature.² δ_{H} 7.19-7.13 (m, 4H), 7.11 (d, $J = 8.0$ Hz, 2H), 6.95 (d, $J = 8.0$ Hz, 2H), 4.37 (s, 1H), 3.52 (t, $J = 5.5$ Hz, 2H), 3.00 (t, $J = 5.5$ Hz, 2H), 2.29 (s, 3H). δ_{C} 148.8, 134.9, 134.7, 129.9, 128.8, 128.7, 126.7, 126.5, 126.2, 116.1, 51.7, 47.5, 29.3, 20.6.

2-(4-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (3c)



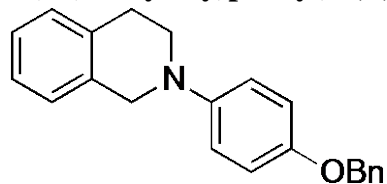
1-Iodo-4-methoxybenzene (116.9 mg, 0.5 mmol) was treated according to general procedure A. Purification by recrystallisation (EtOH) afforded the *title compound* **3c** (107.6 mg, 90%) as a white solid. Spectroscopic data matched those previously reported in the literature.² δ_{H} 7.21-7.10 (m, 4H), 7.01 (d, $J = 9.4$ Hz, 2H), 6.90-6.85 (m, 2H), 4.31 (m, 2H), 3.78 (s, 3H), 3.46 (t, $J = 5.9$ Hz, 2H), 3.00 (t, $J = 5.9$ Hz, 2H). δ_{C} 153.7, 145.5, 134.8, 134.7, 128.9, 126.7, 126.5, 126.1, 118.2, 114.8, 55.8, 52.9, 48.7, 29.3.

2-(2-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (3d)



1-Iodo-2-methylbenzene (116.9.9 mg, 0.5 mmol) was treated according to general procedure A. Purification by flash chromatography on neutral alumina (5:95 EtOAc/*n*-heptane) afforded the *title compound* **3d** (52.6 mg, 44%) as a pale yellow oil. Spectroscopic data matched those previously reported in the literature.² δ_{H} 7.18-7.08 (m, 4H), 7.01 (d, $J = 7.6$ Hz, 2H), 6.94-6.88 (m, 2H), 4.30 (s, 2H), 3.90 (s, 3H), 3.41 (t, $J = 6.2$ Hz, 2H), 2.99 (t, $J = 6.2$ Hz, 2H). δ_{C} 152.8, 141.3, 134.7, 134.4, 129.1, 126.7, 126.3, 125.9, 123.1, 121.1, 119.1, 111.4, 55.7, 53.3, 49.2, 29.1.

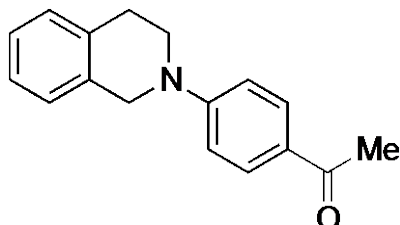
2-(4-(Benzyloxy)phenyl)-1,2,3,4-tetrahydroisoquinoline (3e)



1-(Benzyloxy)-4-iodobenzene (154.9 mg, 0.5 mmol) was treated according to general procedure A. Purification by recrystallisation (EtOH) afforded the *title compound* **3e** (94.5 mg, 60%) as a white solid. Spectroscopic data matched those previously

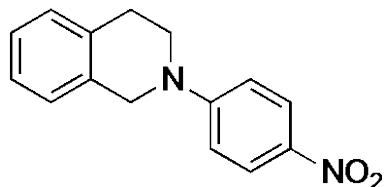
reported in the literature.² ν_{\max} (neat)/ cm^{-1} 3034, 2828, 1511, 1453. δ_{H} 7.45-7.29 (m, 5H), 7.19-7.11 (m, 4H), 6.99-6.93 (m, 4H), 5.03 (s, 2H), 4.31 (s, 2H), 3.46 (t, $J = 5.8$ Hz, 2H), 2.99 (t, $J = 5.8$ Hz, 2H). δ_{C} 153.0, 145.9, 137.8, 134.91, 134.89, 129.0, 128.9, 128.2, 127.8, 126.8, 126.6, 126.2, 118.2, 116.0, 70.9, 52.8, 48.6, 29.4. m/z (HRMS ESI) 316.1699; $[\text{C}_{22}\text{H}_{22}\text{NO}]^+$ requires 316.1696.

1-(4-(3,4-Dihydroisoquinolin-2(1H)-yl)phenyl)ethanone (3f)



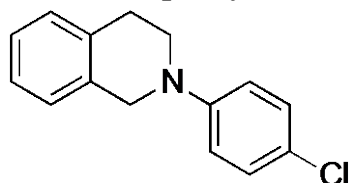
1-(4-Iodophenyl)ethanone (122.9 mg, 0.5 mmol) was treated according to general procedure A. Purification by flash chromatography (20:80 EtOAc/*n*-heptane) afforded the *title compound* **3f** (70.3 mg, 56%) as a pale yellow solid. Spectroscopic data matched those previously reported in the literature.³ ν_{\max} (neat)/ cm^{-1} 2824, 1652, 1588. δ_{H} 7.93-7.89 (m, 2H), 7.24-7.18 (m, 4H), 6.91-6.87 (m, 2H), 4.56 (s, 2H), 3.68 (t, $J = 5.6$ Hz, 2H), 3.01 (t, $J = 5.6$ Hz, 2H), 2.59 (s, 3H). δ_{C} 196.5, 153.1, 135.1, 133.8, 130.7, 128.9, 126.9, 126.66, 126.63, 126.58, 112.1, 49.1, 44.9, 29.1, 26.2. m/z (HRMS ESI) 252.1381; $[\text{C}_{17}\text{H}_{18}\text{NO}]^+$ requires 252.1383.

2-(4-Nitrophenyl)-1,2,3,4-tetrahydroisoquinoline (3g)



1-Iodo-4-nitrobenzene (124.4 mg, 0.5 mmol) was treated according to general procedure A. Purification by flash chromatography (10:90:1 EtOAc/*n*-heptane/ Et_3N) afforded the *title compound* **3g** (85.1 mg, 67%) as a yellow solid. Spectroscopic data matched those previously reported in the literature.⁴ δ_{H} 8.19-8.15 (m, 2H), 7.25-7.18 (m, 4H), 6.85-6.81 (m, 2H), 4.58 (s, 2H), 3.71 (t, $J = 5.9$ Hz, 2H), 3.03 (t, $J = 5.9$ Hz, 2H). δ_{C} 154.1, 137.9, 135.2, 133.4, 128.4, 127.5, 127.0, 126.8, 126.5, 111.5, 49.2, 45.1, 29.3.

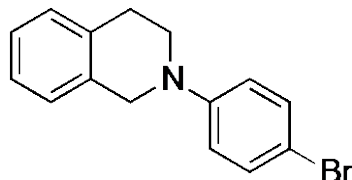
2-(4-Chlorophenyl)-1,2,3,4-tetrahydroisoquinoline (3h)



1-Chloro-4-iodobenzene (118.9 mg, 0.5 mmol) was treated according to general procedure A. Purification by recrystallisation (EtOH) afforded the *title compound* **3h**

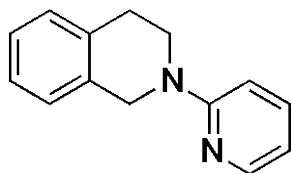
(70.5 mg, 58%) as a pale yellow solid. Spectroscopic data matched those previously reported in the literature.² δ_{H} 7.24-7.16 (m, 6H), 6.92-6.88 (m, 2H), 4.38 (s, 2H), 3.54 (t, $J = 6.1$ Hz, 2H), 2.98 (t, $J = 6.1$ Hz, 2H). δ_{C} 149.3, 135.0, 134.4, 129.6, 129.3, 128.9, 126.8, 126.5, 123.8, 116.5, 51.0, 46.9, 29.2

2-(4-Bromophenyl)-1,2,3,4-tetrahydroisoquinoline (**3i**)



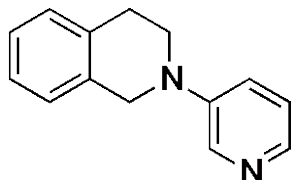
1-Bromo-4-iodobenzene (140.9 mg, 0.5 mmol) was treated according to general procedure A. Purification by flash chromatography (5:95 EtOAc/*n*-heptane) afforded the *title compound* **3i** (28.7 mg, 20%) as a pale yellow solid. Spectroscopic data matched those previously reported in the literature.² δ_{H} 7.37-7.33 (m, 2H), 7.21-7.13 (m, 4H), 6.85-6.80 (m, 2H), 4.38 (s, 2H), 3.53 (t, $J = 5.9$ Hz, 2H), 2.98 (t, $J = 5.9$ Hz, 2H). δ_{C} 149.8, 135.1, 134.4, 132.2, 129.7, 128.8, 126.9, 126.5, 116.8, 110.8, 50.8, 46.7, 29.3.

2-(Pyridin-2-yl)-1,2,3,4-tetrahydroisoquinoline (**3j**)



2-Bromopyridine (78.5 mg, 0.5 mmol) was treated according to general procedure B. Purification by flash chromatography (10:90:1 EtOAc/*n*-heptane/Et₃N) afforded the *title compound* **3j** (73.5 mg, 70%) as a white solid. Spectroscopic data matched those previously reported in the literature.⁵ δ_{H} 8.22 (dd, $J = 4.9, 1.2$ Hz, 1H), 7.52-7.47 (m, 1H), 7.22-7.17 (m, 4H), 6.68 (d, $J = 8.6$ Hz, 1H), 6.60 (dd, $J = 7.1, 4.9$ Hz, 1H), 4.71 (s, 3H), 3.85 (t, $J = 5.8$ Hz, 2H), 2.97 (t, $J = 5.8$ Hz, 2H). δ_{C} 158.8, 148.1, 137.5, 135.5, 134.5, 128.5, 126.7, 126.5, 126.3, 112.6, 106.7, 47.3, 42.6, 29.1.

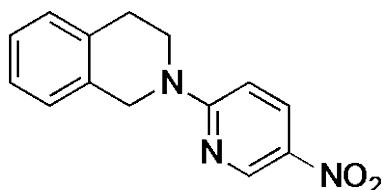
2-(Pyridin-3-yl)-1,2,3,4-tetrahydroisoquinoline (**3l**)



3-Bromopyridine (78.5 mg, 0.5 mmol) was treated according to general procedure B. Purification by flash chromatography (10:90:1→30:70:1 EtOAc/*n*-heptane/Et₃N) afforded the *title compound* **3l** (65.1 mg, 62%) as a pale yellow oil. ν_{max} (neat)/cm⁻¹ 3036, 2921, 1708, 1660, 1459, 1231. δ_{H} 8.36 (d, $J = 2.7$ Hz, 1H), 8.06 (dd, $J = 4.4, 1.5$ Hz, 1H), 7.24-7.16 (m, 6H), 4.44 (s, 2H), 3.59 (t, $J = 5.9$ Hz, 2H), 3.00 (t, $J = 5.9$

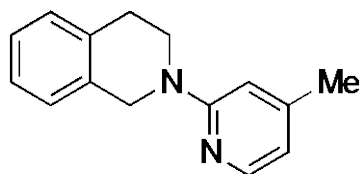
Hz, 2H). δ_C 146.2, 139.6, 137.4, 134.6, 133.7, 128.6, 126.7, 126.6, 126.3, 123.6, 121.1, 49.9, 45.8, 28.9. m/z (HRMS ESI) 211.1230; $[C_{14}H_{15}N_2]^+$ requires 211.1230.

2-(5-Nitropyridin-2-yl)-1,2,3,4-tetrahydroisoquinoline (**3m**)



2-Bromo-5-nitropyridine (100.9 mg, 0.5 mmol) was treated according to general procedure B. Purification by flash chromatography (20:80:1 EtOAc/*n*-heptane/Et₃N) afforded the *title compound* **3m** (48.4 mg, 38%) as a yellow solid. ν_{\max} (neat)/cm⁻¹ 2922, 1596, 1331, 1296. δ_H 9.11 (d, $J = 2.5$ Hz, 1H), 8.26 (dd, $J = 9.5, 2.8$ Hz, 1H), 7.28-7.24 (m, 4H), 6.62 (d, $J = 9.5$ Hz, 1H), 4.88 (s, 2H), 3.97 (t, $J = 5.8$ Hz, 2H), 3.03 (t, $J = 5.8$ Hz, 2H). δ_C 160.1, 146.6, 135.08, 135.06, 133.1, 133.0, 128.3, 127.2, 126.8, 126.6, 104.6, 47.1, 43.1, 28.9. m/z (HRMS ESI) 278.0899; $[C_{14}H_{13}N_3O_2Na]^+$ requires 278.0900.

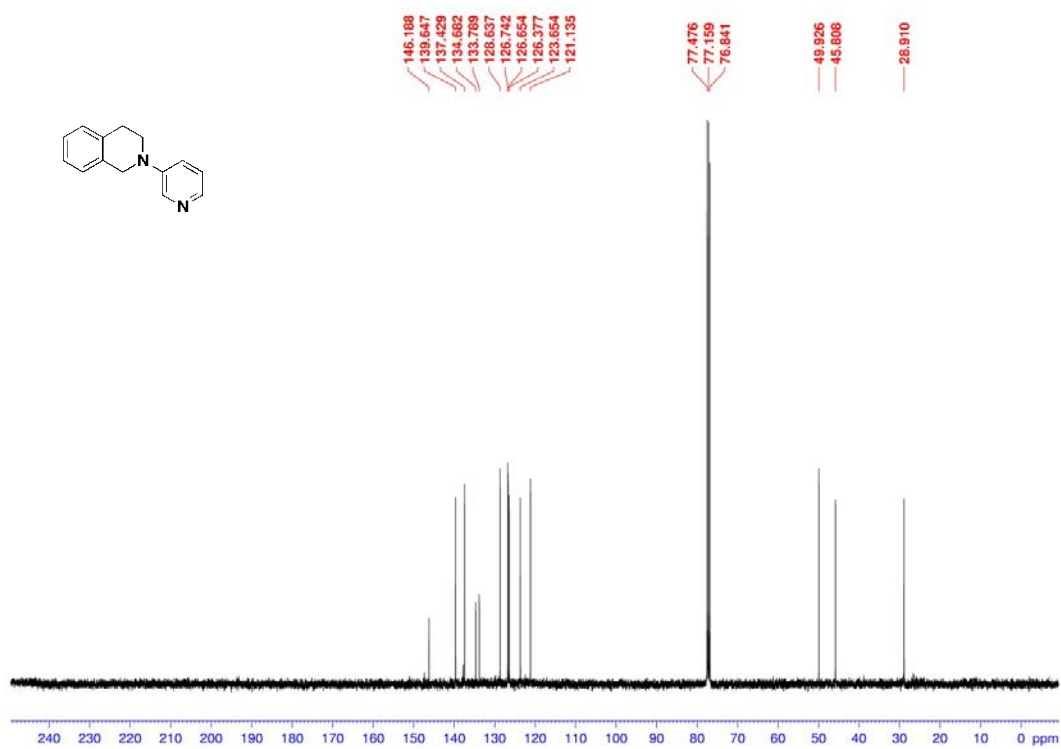
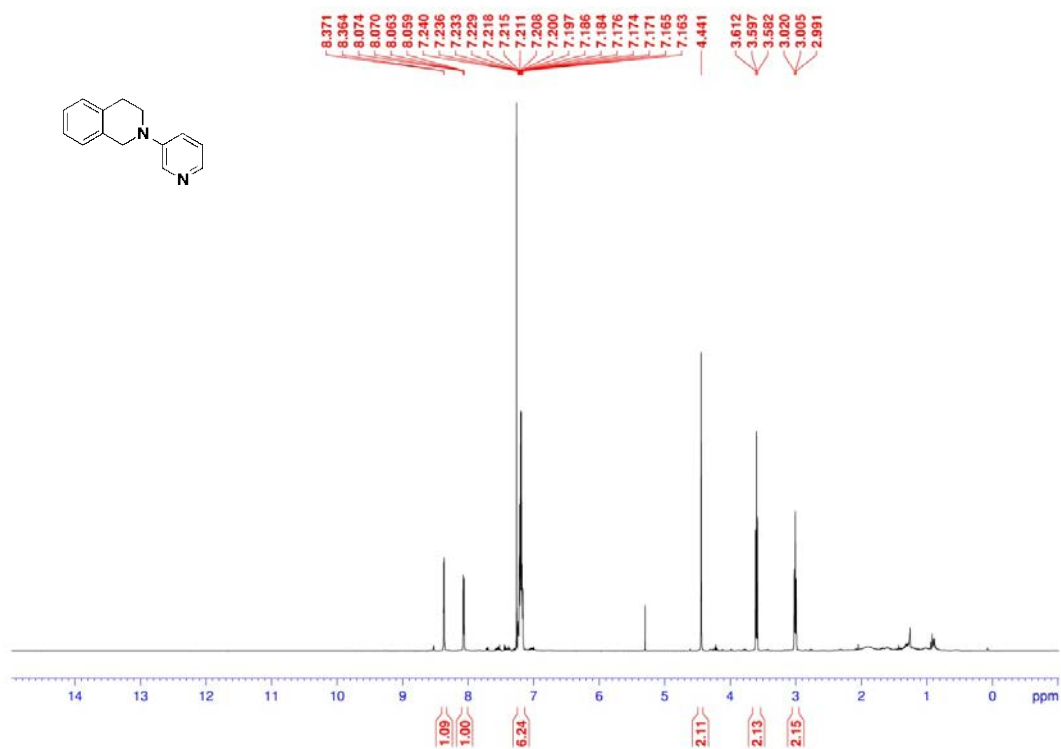
2-(4-Methylpyridin-2-yl)-1,2,3,4-tetrahydroisoquinoline (**3n**)



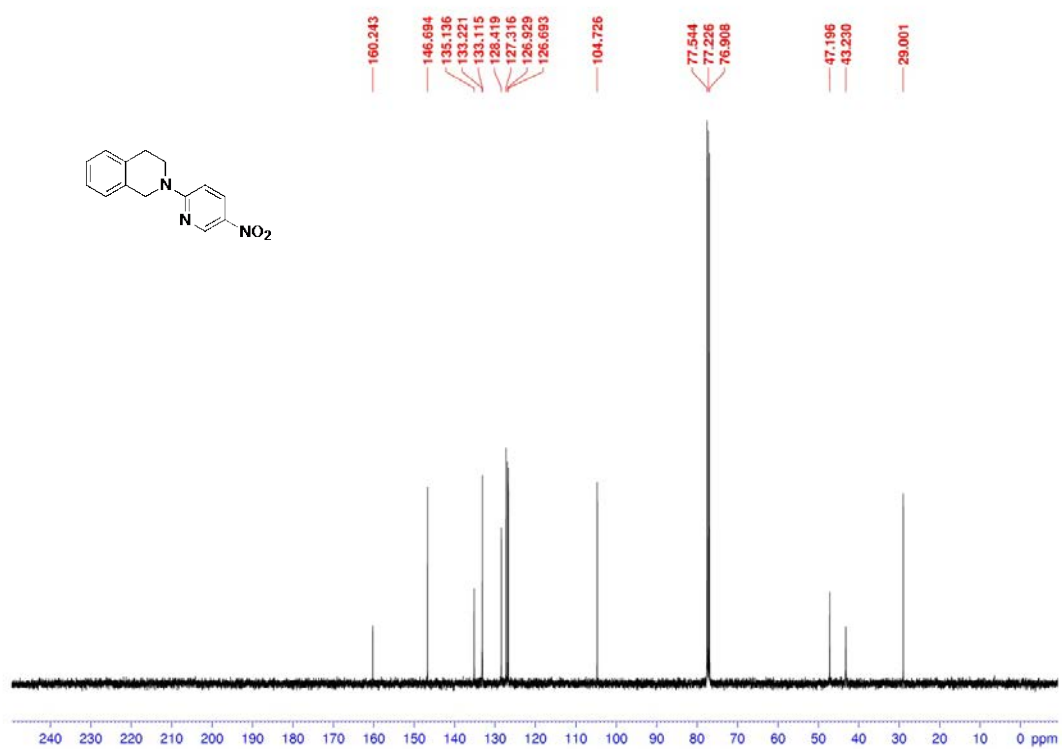
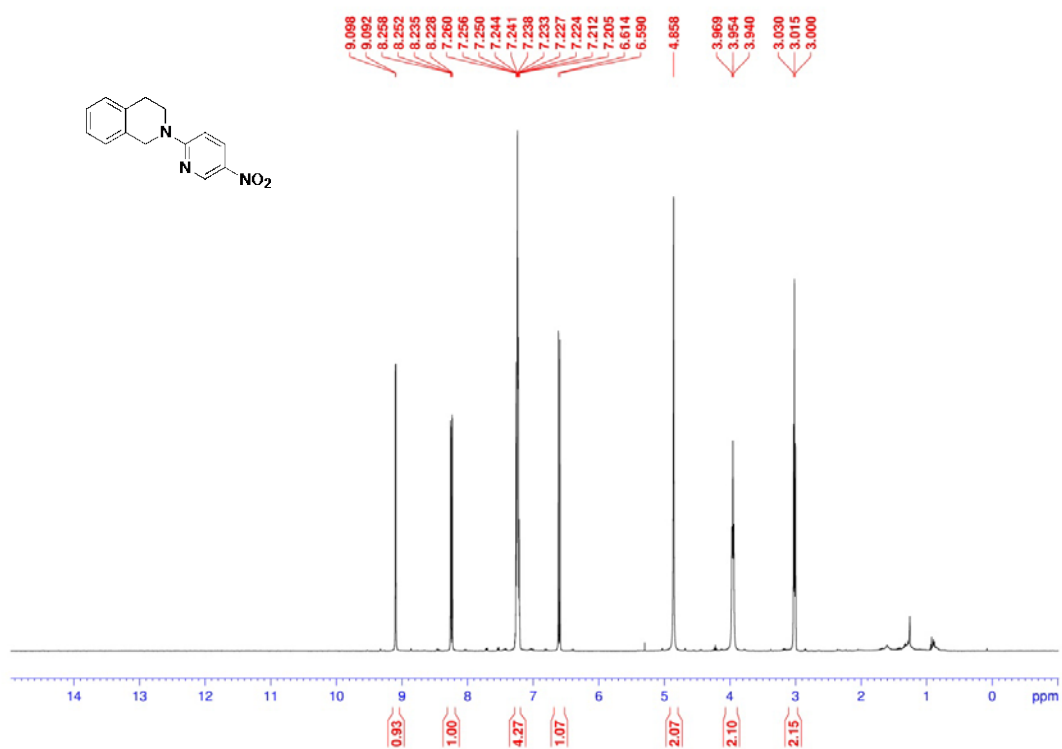
2-Bromo-4-methylpyridine (85.5 mg, 0.5 mmol) was treated according to general procedure B. Purification by preparative TLC (2:98:0.1 EtOAc/*n*-heptane/Et₃N) afforded the *title compound* **3n** (67.2 mg, 60%) as a white solid. ν_{\max} (neat)/cm⁻¹ 2921, 1664, 1602. δ_H 8.08 (d, $J = 5.1$ Hz, 1H), 7.22-7.17 (m, 4H), 6.50 (s, 1H), 6.46 (d, $J = 5.1$ Hz, 1H), 4.69 (s, 2H), 3.84 (t, $J = 5.8$ Hz, 2H), 2.97 (t, $J = 5.8$ Hz, 2H), 2.29 (s, 3H). δ_C 159.2, 148.4, 147.7, 135.5, 134.5, 128.5, 126.7, 126.4, 126.2, 114.2, 107.2, 47.4, 42.7, 29.2, 21.6. m/z (HRMS ESI) 247.1206; $[C_{15}H_{16}N_2Na]^+$ requires 247.1206.

3. Spectra

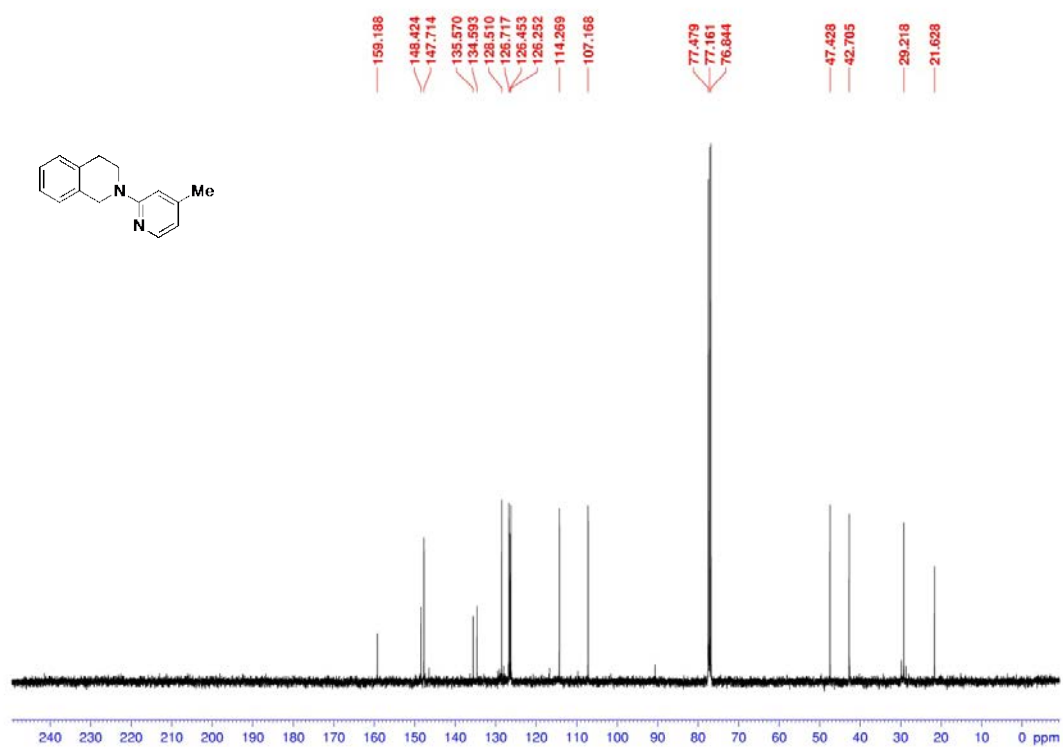
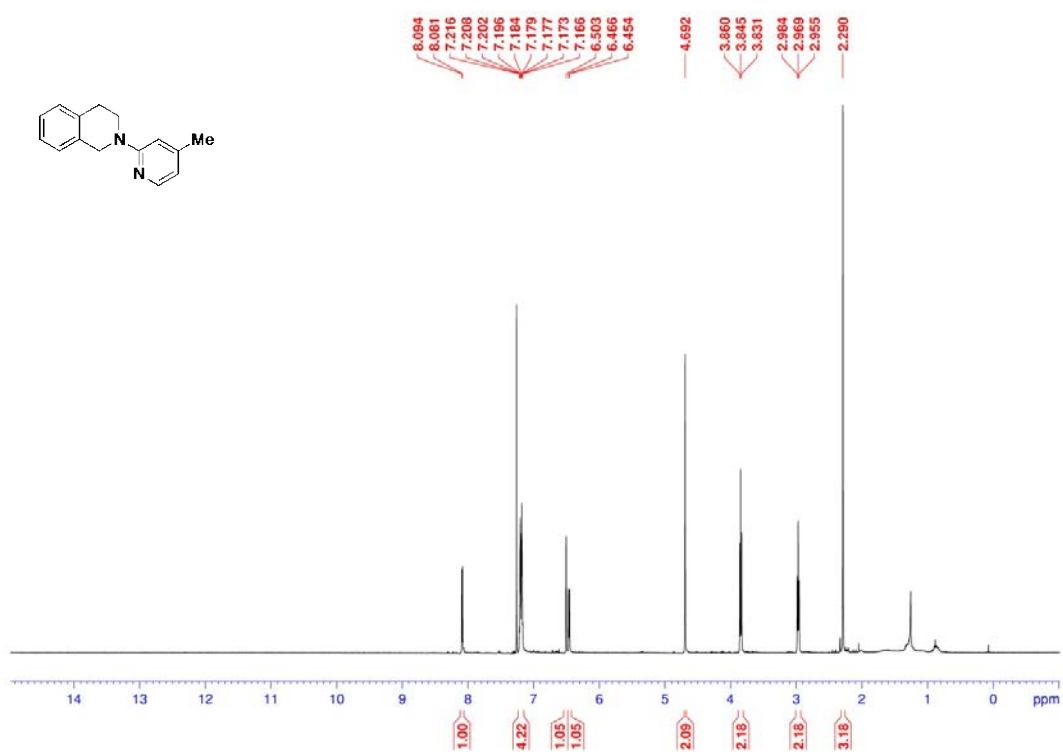
2-(Pyridin-3-yl)-1,2,3,4-tetrahydroisoquinoline (3l)



2-(5-Nitropyridin-2-yl)-1,2,3,4-tetrahydroisoquinoline (3m)



2-(4-Methylpyridin-2-yl)-1,2,3,4-tetrahydroisoquinoline (3n)



4. References

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