New 4-Spiroannulated Tetrahydroisoquinolines by One-Pot Sequential Procedure. Isolation and Characterization of σ -Alkylpalladium Heck Intermediates

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Supporting Information

General

Melting points were measured with a Büchi B-540 heating unit and are uncorrected. IR spectra were recorded on a FT-IR spectrophotometer. Mass spectra were determined on an HPLC-MS LCQ-Advantage Thermo Finnigan instrument. ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz on an AVANCE 400 Bruker. Elemental analyses were executed on Perkin-Elmer CHN Analyzer Series II 2400. Chemical shifts (δ) are given as ppm relative to the residual solvent peak (chloroform-*d*1 7.25 ppm/77 ppm). Column chromatography was performed on a Merck silica gel 60, (mesh size 63-200 μm).

General one-pot procedure for the preparation of spiro[isoquinoline-4,5'-isoxazole]

4a-d.

A solution of **2** (1 mmol) and TEA (0,17 ml, 1.2 mmol) in DMF (3 ml) was dropped in a stirred solution of **1** (309 mg, 1 mmol) in DMF (3 mL). The resulting solution was heated at 60°C for 45 min, then $\text{Pd}(\text{OAc})_2$ (11 mg, 0.05 mol%), PPh_3 (52 mg, 0.20 mol%) and Cs_2CO_3 (650 mg, 2 mmol) were added in sequence. The mixture was taken to 120°C for 6 h. Finally, **3** (276 mg, 1,2 mmol) was added and the mixture was stirred at 120°C for 18 h. After concentration of the solvent under reduced pressure, the crude brown residue was purified by flash chromatography (EtPe / AcOEt 15:1).

3'-(3,5-Dichloro-2,4,6-trimethylphenyl)-2-methyl-1,2,3,4'-tetrahydro-spiro[isoquinoline-4,5'-isoxazole] (4a) – Yield: 30%. M.p. 169-170°C (diisopropyl ether). ^1H NMR (400 MHz, CDCl_3) δ : 2.40 (6H, s), 2.53 (3H, s), 2.56 (3H, s), 2.84, 2.94 (2H, AB system, $J = 11.2$ Hz), 3.29, 3.45 (2H, AB system, $J = 18.4$ Hz), 3.53, 3.81 (2H, AB system, $J = 15.0$ Hz), 7.09 (1H, d, $J = 7.5$ Hz), 7.28 (1H, dd, $J = 7.3, 7.5$ Hz), 7.35 (1H, dd, $J = 7.3, 7.6$ Hz), 7.56 (1H, d, $J = 7.6$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 18.6 (q), 19.4 (q), 46.6 (q), 54.1 (t), 58.2 (t), 63.3 (t), 85.7 (s), 126.1 (d), 126.4 (d), 127.8 (d), 128.3 (d), 129.3 (s), 133.6 (s), 134.0 (s), 135.2 (s), 135.9 (s), 137.2 (s), 156.5 (s). MS: m/z 388 (M^+). Anal. calcd for $\text{C}_{21}\text{H}_{22}\text{Cl}_2\text{N}_2\text{O}$: C, 64.79; H, 5.70; N, 7.20. Found C, 64.90; H, 5.41; N, 6.93.

2-Allyl-3'-(3,5-dichloro-2,4,6-trimethylphenyl)-1,2,3,4'-tetrahydro-spiro[isoquinoline-4,5']-

isoxazole] (4b) – Yield: 32%. M.p. 132-133°C (diisopropyl ether). ¹H NMR (400 MHz, CDCl₃) δ: 2.39 (6H, s), 2.56 (3H, s), 2.71 (1H, d, *J* = 11.1 Hz), 3.10-3.17 (2H, m), 3.25, 3.46 (2H, AB system, *J* = 18.3 Hz), 3.32-3.36 (1H, m), 3.61, 3.99 (2H, AB system, *J* = 14.9 Hz), 5.27 (1H, d, *J* = 10.2 Hz), 5.31 (1H, d, *J* = 17.3 Hz), 5.85-6.01 (1H, m), 7.10 (1H, d, *J* = 7.6 Hz), 7.28 (1H, dd, *J* = 7.7, 7.8 Hz), 7.35 (1H, dd, *J* = 7.8, 7.6 Hz), 7.57 (1H, d, *J* = 7.7 Hz); ¹³C NMR (100 MHz, CDCl₃) δ: 18.6 (q), 19.4 (q), 54.2 (t), 56.6 (t), 59.5 (t), 61.3 (t), 85.9 (s), 85.9 (s), 119.3 (t), 126.1 (d), 126.5 (d), 127.8 (d), 128.3 (d), 129.4 (s), 133.6 (s), 134.0 (s), 135.0 (d), 135.4 (s), 135.9 (s), 137.8 (s), 156.7 (s). MS: *m/z* 414 (M⁺). Anal. calcd for C₂₃H₂₄Cl₂N₂O: C, 66.51; H, 5.82; N, 6.74. Found C, 66.34; H, 6.07; N, 6.91.

2-Cyclohexyl-3'-(3,5-dichloro-2,4,6-trimethylphenyl)-1,2,3,4'-tetrahydro-spiro[isoquinoline-4,5']-

isoxazole] (4c) – Yield: 45%. M.p. 177-178°C (diisopropyl ether) ¹H NMR (400 MHz, CDCl₃) δ: 1.03-1.47 (6H, m), 1.65-2.25 (4H, m), 2.41 (6H, s), 2.50-2.57 (1H, m), 2.56 (3H, s), 2.82, 3.14 (2H, AB system, *J* = 11.1 Hz), 3.22, 3.53 (2H, AB system, *J* = 18.4 Hz), 3.85, 3.92 (2H, AB system, *J* = 15.0), 7.09 (1H, d, *J* = 7.5 Hz), 7.26 (1H, dd, *J* = 7.4, 7.7 Hz), 7.32 (1H, dd, *J* = 7.4, 7.5 Hz), 7.55 (1H, d, *J* = 7.7 Hz); ¹³C NMR (100 MHz, CDCl₃) δ: 18.6 (q), 19.4 (q), 26.1 (t), 26.3 (t), 26.7 (t), 28.1 (t), 30.4 (t), 52.9 (t), 54.2 (t), 55.8 (t), 63.3 (d), 86.5 (s), 126.0 (d), 126.6 (d), 127.5 (d), 128.0 (d), 129.5 (s), 133.6 (s), 134.0 (s), 135.8 (s), 136.0 (s), 138.3 (s), 156.7 (s). MS: *m/z* 456 (M⁺). Anal. calcd for C₂₆H₃₀Cl₂N₂O: C, 68.27; H, 6.61; N, 6.12. Found C, 68.25; H, 6.79; N, 6.22.

2-Cyclopentyl-3'-(3,5-dichloro-2,4,6-trimethylphenyl)-1,2,3,4'-tetrahydro-spiro[isoquinoline-

4,5'-isoxazole] (4d) – Yield: 41%. M.p. 191-192°C (diisopropyl ether). ¹H NMR (400 MHz, CDCl₃) δ: 1.42-1.56 (2H, m), 1.57-1.78 (4H, m), 1.80-2.05 (2H, m), 2.41 (6H, s), 2.56 (3H, s), 2.82-2.90 (1H, m), 2.73, 3.21 (2H, AB system, *J* = 11.3 Hz), 3.25, 3.51 (2H, AB system, *J* = 18.4 Hz), 3.59, 3.98 (2H, AB system, *J* = 14.9), 7.10 (1H, d, *J* = 7.5 Hz), 7.27 (1H, dd, *J* = 7.3, 7.5 Hz), 7.34 (1H, dd, *J* = 7.3, 7.6 Hz), 7.56 (1H, d, *J* = 7.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ: 18.6 (q), 19.4 (q), 24.4 (t), 24.5 (t), 30.7 (t), 31.1 (t), 54.2 (t), 55.7 (t), 59.0 (t), 66.8 (d), 86.0 (s), 126.0 (d), 126.6 (d), 127.7 (d), 128.2 (d),

129.4 (s), 133.6 (s), 134.0 (s), 135.7 (s), 135.9 (s), 137.9 (s), 156.7 (s). MS: m/z 442 (M^+). Anal. calcd for $C_{25}H_{28}Cl_2N_2O$: C, 67.72; H, 6.36; N, 6.32. Found C, 67.71; H, 6.57; N, 6.09.

General procedure for the preparation of the 4-methylene-1,2,3,4-tetrahydro-isoquinolines 6a-c from palladacycles 9a-c.

A solution of **9a-c** (1 mmol) and TEA (0.42 ml, 3 mmol) in CH_3CN (10 mL) was refluxed for 48h. After removal of the solvent under reduced pressure, H_2O (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 ml). The combined organic layers were dried (Na_2SO_4) and eluted through a silica gel column (EtPe / AcOEt 15:1).

2-Methyl-4-methylene-1,2,3,4-tetrahydro-isoquinoline (6a) – Yield: 38%. Oil. 1H NMR (400 MHz, $CDCl_3$) δ : 2.46 (3H, s), 3.35 (2H, s), 3.68 (2H, s), 5.04 (1H, s), 5.64 (1H, s), 7.06-7.09 (1H, m), 7.18-7.24 (2H, m), 7.69-7.72 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 45.6 (q), 59.0 (t), 60.7 (t), 108.1 (t), 123.8 (d), 127.0 (d), 127.1 (d), 128.2 (d), 132.2 (s), 135.2 (s), 140.0 (s). MS: m/z 159 (M^+). Anal. calcd for $C_{11}H_{13}N$: C, 82.97; H, 8.23; N, 8.80. Found C, 82.79; H, 7.97; N, 8.54.

2-Allyl-4-methylene-1,2,3,4-tetrahydro-isoquinoline (6b) – Yield: 41%. Oil. 1H NMR (400 MHz, $CDCl_3$) δ : 3.19 (2H, d, $J = 6.5$ Hz), 3.42 (2H, s), 3.76 (2H, s), 5.03 (1H, s), 5.23 (1H, d, $J = 10.2$ Hz), 5.27 (1H, d, $J = 17.2$ Hz), 5.64 (1H, s), 5.95 (1H, tdd, $J = 6.5, 10.2, 17.2$ Hz), 7.06-7.10 (1H, m), 7.19-7.23 (2H, m), 7.68-7.72 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 56.8 (t), 58.4 (t), 60.7 (t), 108.4 (t), 118.6 (t), 123.8 (d), 127.0 (d), 127.3 (d), 128.3 (d), 132.6 (s), 135.0 (s), 135.5 (d), 139.6 (s). MS: m/z 185 (M^+). Anal. calcd for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56. Found C, 84.24; H, 7.91; N, 7.29.

2-Cyclohexyl-4-methylene-1,2,3,4-tetrahydro-isoquinoline (6c) – Yield: 46%. Oil. 1H NMR (400 MHz, $CDCl_3$) δ : 1.10-2.05 (10H, m), 2.47-2.53 (1H, m), 3.51 (2H, s), 3.89 (2H, s), 5.01 (1H, s), 5.60 (1H, s), 7.07-7.11 (1H, m), 7.17-7.24 (2H, m), 7.66-7.71 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 26.2 (t), 26.7 (t), 29.5 (t), 53.0 (t), 55.1 (t), 62.4 (d), 107.7 (t), 123.9 (d), 126.8 (d), 127.3 (d), 129.1 (d), 132.9 (s), 135.9 (s). MS: m/z 227 (M^+). Anal. calcd for $C_{16}H_{21}N$: C, 84.53; H, 9.31; N, 6.16. Found C, 84.24; H, 9.54; N, 6.19.

General procedure for the preparation of the palladacycles 9a-c with stoichiometric amount of Pd(PPh₃)₄.

To a solution of **5a-c** (1 mmol) in CH₃CN (10 mL) were added Pd(PPh₃)₄ (1,15 g, 1 mmol) and TEA (0,42 ml, 3 mmol). The mixture was heated and stirred at reflux for 24h. After removal of the solvent under reduced pressure, H₂O (10 mL) was added and the aqueous layer was extracted with CH₂Cl₂ (2 x 10 ml) The combined organic layers were dried (Na₂SO₄) and eluted through a silica gel column (EtPe / AcOEt 7:3).

Compound 9a - Yield: 55%. M.p. 128-130°C (diisopropyl ether). ¹H NMR (400 MHz, CDCl₃) δ: 1.56 (1H, m), 1.84 (1H, dd, *J* = 3.0, 9.2 Hz), 2.62 (1H, m), 2.71 (1H, d, *J* = 10.2 Hz), 3.01 (1H, d, *J* = 10.2 Hz), 3.28 (3H, d, *J* = 2.8 Hz), 3.62 (1H, dd, *J* = 5.8, 14.8 Hz), 5.11 (1H, d, *J* = 14.8 Hz), 6.98 (1H, d, *J* = 7.3 Hz), 7.18-7.39 (18H, m); ¹³C NMR (100 MHz, CDCl₃) δ: 45.6 (d), 50.7 (t), 53.1 (q), 63.2 (t), 65.3 (t), 126.7 (d), 127.1 (d), 127.4 (d), 128.1 (d), 128.2 (d), 128.3 (d), 130.4 (d), 132.2 (s) 132.5 (s), 132.6 (s), 135.0 (d), 135.1 (d), 140.2 (s). MS: *m/z* 655 (M⁺) calculated for the most abundant Pd isotope, ¹⁰⁶Pd. Anal. calcd for C₂₉H₂₉INPPd: C, 53.11; H, 4.46; N, 2.14. Found C, 52.97; H, 4.76; N, 1.88.

Compound 9b - Yield: 66%. M.p. 163-165°C (diisopropyl ether). ¹H NMR (400 MHz, CDCl₃) δ: 1.49-1.53 (1H, m), 1.83 (1H, dd, *J* = 3.2, *J* = 9.1 Hz), 2.43 (1H, d, *J* = 10.4 Hz), 2.61-2.64 (1H, m), 3.13-3.22 (1H, m), 3.23 (1H, d, *J* = 10.4 Hz), 3.81 (1H, dd, *J* = 5.5, *J* = 14.7 Hz), 4.89 (1H, dd, *J* = 2.8, *J* = 9.9 Hz), 5.17 (1H, d, *J* = 14.7 Hz), 5.43 (1H, d, *J* = 17.3 Hz), 5.47 (1H, d, *J* = 10.3 Hz), 6.65-6.71 (1H, m), 6.98 (1H, d, *J* = 7.4 Hz), 7.20-7.38 (18H, m); ¹³C NMR (100 MHz, CDCl₃) δ: 45.35 (d), 50.41 (t), 60.24 (t), 61.97 (t), 64.88 (t), 121.02 (t), 126.67 (d), 127.21 (d), 127.45 (d), 128.07 (d), 128.22 (d), 128.33 (d), 130.43 (d), 132.26 (s), 132.75 (s), 134.42 (d), 134.95 (d), 135.06 (d), 140.83 (s). MS: *m/z* 681 (M⁺). Anal. calcd for C₃₁H₃₁INPPd: C, 54.60; H, 4.58; N, 2.05. Found C, 54.41; H, 4.81; N, 1.77.

Compound 9c - Yield: 59%. M.p. 158-160°C (diisopropyl ether). ¹H NMR (400 MHz, CDCl₃) δ: 1.10-1.93 (10H, m), 2.13 (1H, d, *J* = 11.5 Hz), 2.57 (1H, d, *J* = 10.2 Hz), 2.65-2.68 (1H, m), 2.97 (1H, d, *J* =

10.2 Hz), 3.18-3.24 (1H, m), 3.93-4.00 (1H, m), 4.32 (1H, dd, $J = 6.2, 14.6$ Hz), 5.03 (1H, d, $J = 14.6$ Hz), 6.95 (1H, d, $J = 7.4$ Hz), 7.15-7.39 (18H, m); ^{13}C NMR (100 MHz, CDCl_3) δ : 25.6 (t), 26.0 (t), 26.9 (t), 30.1 (t), 33.5 (t), 45.9 (d), 49.1 (t), 54.7 (t), 58.4 (t), 65.3 (d), 126.6 (d), 127.1 (d), 127.4 (d), 127.9 (d), 128.3 (d), 128.4 (d), 130.3 (d), 132.5 (s), 133.0 (s), 133.6 (s), 134.9 (d), 135.0 (d), 140.9 (s). MS: m/z 723 (M^+). Anal. calcd for $\text{C}_{34}\text{H}_{37}\text{INPPd}$: C, 56.41; H, 5.15; N, 1.93. Found C, 56.16; H, 5.29; N, 2.20.

Crystallography: The crystallographic measurements were performed using an Enraf-Nonius CAD4 automated diffractometer, equipped with graphite-monochromated Mo- $\text{K}\alpha$ radiation ($\lambda = 0.71073$ Å). Generator settings: 50 kV, 30 mA. A specimen of suitable size and quality was selected and glued on the tip of a glass fiber. The structures were solved by direct methods (SHELX86), which successfully located most of the non-hydrogen atoms. Subsequent refinement on F^2 using the SHELX97 as implemented in the WINGX suite of programs allowed location of the remaining non-hydrogen atoms. These were eventually inserted as atoms riding on the pertinent carbon atoms. Crystal data, details of the refinement procedure and final agreement factors, together with the full list of fractional atomic coordinates can be found in the pertinent CIF file. CCDC 613934.

ORTEP drawing of compound **9b**. Thermal ellipsoids are drawn at the 50% probability level. Hydrogen atoms are given with arbitrary radii.

Crystal data: Triclinic, space group P-1 (No. 2), $a = 9.458(2)$; $b = 11.332(2)$; $c = 13.604(2)$ Å, $\alpha = 76.51(1)$; $\beta = 86.68(2)$; $\gamma = 82.32(2)$ °; $V = 1404.6(4)$ Å³, $Z = 2$.

^1H -NMR spectrum of compound **4a**.

^{13}C -NMR spectrum of compound **4a**.

^1H -NMR spectrum of compound **4b**.

^{13}C -NMR spectrum of compound **4b**.

^1H -NMR spectrum of compound **4c**.

^{13}C -NMR spectrum of compound **4c**.

^1H -NMR spectrum of compound **4d**.

^{13}C -NMR spectrum of compound **4d**.

^1H -NMR spectrum of compound **6a**.

^{13}C -NMR spectrum of compound **6a**.

^1H -NMR spectrum of compound **6b**.

^{13}C -NMR spectrum of compound **6b**.

^1H -NMR spectrum of compound **6c**.

^{13}C -NMR spectrum of compound **6c**.

^1H -NMR spectrum of compound **9a**.

^{13}C -NMR spectrum of compound **9a**.

^1H -NMR spectrum of compound **9b**.

^{13}C -NMR spectrum of compound **9b**.

^1H -NMR spectrum of compound **9c**.

^{13}C -NMR spectrum of compound **9c**.