Supporting information

New Synthetic Approach for the Preparation of 1-Aryl-3,4-dihydro-isoquinolines by Liebeskind-Sorgl Reaction.

Péter Ábrányi-Balogh, a,b Péter Slégel, a Balázs Volk, a László Pongó, a Mátéás Mileš a,b.

a Egis Pharmaceuticals Plc., Chemical Research Division, P.O. Box 100, H-1475 Budapest, Hungary
b Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, P.O. Box 91, H-1521 Budapest, Hungary

General remarks

Commercially available reagents were purchased from Sigma-Aldrich and were used without further purification. All melting points were measured with a Kofler-Boëtius microapparatus and are uncorrected. 1H and 13C NMR spectra were recorded with a Varian Unity Inova 500 spectrometer (500 and 125 MHz for 1H and 13C NMR spectra, respectively) or with a Bruker Avance III spectrometer (400 and 100 MHz for 1H and 13C NMR spectra, respectively). DMSO-d6 or CDCl3 was used as the solvent, and TMS was used as the internal standard.

The FT-IR spectra of KBr pellets or neat samples were recorded with a Bruker Vector 22 spectrometer. Mass spectra were recorded on a Waters Micromass Q-TOF Premier spectrometer coupled to a Waters Acuity UPLC system consisting of a Binary Solvent Manager, Sample Manager, Column Manager and a PDA Detector. Chromatographic column was a Waters Acuity BEH C18 column with dimensions of 2.1 x 50 mm. Eluent A was 5% acetonitrile in 0.1 M ammonium acetate, eluent B was acetonitrile. 5 min gradient elution was used initial: 10% B, 3 min: 90% B. Accurate mass measurements were locked internally against the peak at m/z = 556.2771 of Leucine enkephaline.

Characterization data for known compounds

1-Phenyl-3,4-dihydroisoquinoline (3a).

Yield 0.16 g (78%), yellow oil. IR (film, cm−1): 2929, 1608, 1565, 1020. 1H NMR (CDCl3, 500 MHz): δ 7.60-7.59 (m, 2H), 7.43-7.41 (m, 3H), 7.39-7.36 (m, 1H), 7.27-7.24 (m, 2H), 3.88-3.84 (m, 2H), 2.80 (t, J = 7.1 Hz, 2H) ppm. [lit.31] 13C NMR (CDCl3, 500 MHz): δ 174.85 (m, 2H), 172.7-172.38 (m, 4H), 17.12-17.21 (m, 3H) 3.77 (t, J = 7.3 Hz, 2H), 2.72 (t, J = 7.3 Hz, 2H) ppm. 13C NMR (CDCl3, 125 MHz): δ 167.2, 139.0, 138.8, 130.6, 129.2, 128.7, 128.5, 128.4, 128.1, 127.9, 127.4, 126.5, 47.6, 26.3 ppm. HRMS calcld. for C13H12N [M+H]+ 208.1126; found 208.1133.

1-(4-Methylphenyl)-3,4-dihydroisoquinoline (3b).

Yield 0.18 g (83%), pale yellow crystals, mp 74-76 °C (i-Pr2O). (lit.52 mp 75-76 °C). IR (KBr, cm−1): 3442, 2954, 1606, 1439, 1302, 1185, 1120, 742. 1H NMR (CDCl3, 500 MHz): δ 7.50-7.49 (m, 2H), 7.38-7.35 (m, 1H), 7.29-7.26 (m, 2H), 7.24-7.21 (m, 3H), 3.82 (t, J = 7.2 Hz, 2H), 2.78 (t, J = 7.2 Hz, 2H), 2.40 (s, 3H) ppm. 13C NMR (CDCl3, 125 MHz): δ 167.0, 139.2, 138.9, 136.2, 130.5, 128.9, 128.8, 128.7, 127.9, 127.3, 126.4, 47.6, 26.4 ppm. HRMS calcld. for C13H14N [M+H]+ 222.1294; found 222.1290.

1-(4-Methoxyphenyl)-3,4-dihydroisoquinoline (3c).

Yield 0.19 g (82%), pale yellow crystals, mp 96-97 °C (i-Pr2OH). (lit.52 mp 94-95 °C). IR (KBr, cm−1): 3003, 2841, 1603, 1505, 1246, 1016, 842, 745. 1H NMR (CDCl3, 400 MHz): δ 7.58-7.56 (m, 2H), 7.40-7.36 (m, 1H), 7.31-7.25 (m, 3H), 6.96-6.94 (m, 2H), 3.86 (s, 3H), 3.83-3.79 (m, 2H), 2.78 (t, J = 7.3 Hz, 2H) ppm. 13C NMR (CDCl3, 100 MHz): δ 166.6, 160.6, 139.0, 131.5, 130.5, 130.2, 128.9, 127.9, 127.3, 126.4, 113.4, 55.3, 47.5, 26.4 ppm. HRMS calcld. for C14H15NO [M+H]+ 238.1232; found 238.1224.

1-(3-Dimethoxynaphenyl)-3,4-dihydroisoquinoline (3d).

Yield 0.24 g (88%), yellow crystals, mp 102-104 °C (McCN). IR (KBr, cm−1): 2961, 1513, 1412, 1136, 1024. 1H NMR (CDCl3, 500 MHz): δ 7.40-7.37 (m, 1H), 7.35-7.33 (m, 1H), 7.28-7.27 (m, 1H), 7.26-7.25 (m, 1H), 7.15-7.13 (m, 1H), 6.91-6.89 (m, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.82 (t, J = 7.2 Hz, 2H), 2.79 (t, J = 7.3 Hz, 2H) ppm. [lit.31] 13C NMR (270 MHz, CDCl3): δ 7.50-6.80 (m, 7H), 3.95 (s, 6H), 3.90-3.60 (m, 2H), 2.90-2.65 (m, 2H) ppm. 13C NMR (CDCl3, 125 MHz): δ 166.6, 150.1, 148.8, 139.1, 132.0, 131.7, 130.5, 127.9, 127.3, 126.4, 121.9, 111.8, 110.4, 56.0, 55.9, 47.5, 26.4 ppm. HRMS calcld. for C18H16NO2 [M+H]+ 268.1338; found 268.1333.

1-(4-Benzoxynaphenyl)-3,4-dihydroisoquinoline (3e).

Yield 0.26 g (82%), yellow oil. IR (KBr, cm−1): 2938, 1606, 1510, 1245, 747. 1H NMR (CDCl3, 500 MHz): δ 7.57-7.55 (m, 2H), 7.45-7.44 (m, 2H), 7.40-7.36 (m, 3H), 7.34-7.30 (m, 1H), 7.26-7.24 (m, 2H), 7.02-7.00 (m, 2H), 5.12 (s, 2H), 3.82-3.79 (m, 2H), 2.77 (t, J = 7.2 Hz, 2H) ppm. [lit.31] 13C NMR (400 MHz, CDCl3): δ 7.55 (d, J = 8.9 Hz, 2H), 7.45-7.43 (m, 2H), 7.40-7.29 (m, 6H), 7.26-7.24 (m, 1H), 7.00 (d, J = 8.8 Hz, 2H), 5.11 (s, 2H), 3.81-3.78 (m, 2H), 2.79-2.75 (m, 2H) ppm. 13C NMR (CDCl3, 125 MHz):
δ 166.6, 159.8, 139.0, 136.8, 131.8, 130.5, 130.3, 128.9, 128.6, 128.0, 127.9, 127.4, 127.3, 126.5, 114.4, 70.0, 47.6, 26.4 ppm. HRMS calcd. for C_{12}H_{12}NO [M+H]^+ 314.1545; found 314.1528.

1-[4-(Methylsulfanyl)phenyl]-3,4-dihydroisoquinoline (3m).

Yield 0.16 g (65%), pale yellow crystals, mp 93-95 °C (i-Pr_2O). IR (film, cm⁻¹): 3417, 2940, 1599, 1321, 1091, 745. \(^1\)H NMR (CDCl₃, 400 MHz): δ 7.56-7.54 (m, 2H), 7.41-7.35 (m, 1H), 7.30-7.23 (m, 5H), 3.82 (bs, 2H), 2.78 (s, J = 6.8 Hz, 2H) 2.52 (s, 3H) ppm. \(^13\)C NMR (CDCl₃, 100 MHz): δ 166.8, 140.3, 138.8, 135.5, 130.8, 129.2, 128.7, 128.0, 127.6, 127.4, 126.8, 126.5, 125.7, 124.1, 47.8, 26.3, 15.5 ppm. HRMS: [M⁺] 253.0929, calculated for C_{14}H_{14}NS 253.0925.

1-(4-Chlorophenyl)-3,4-dihydroisoquinoline (3n).

Yield 0.21 g (85%), white crystals, mp 70-71 °C (petroleum ether). IR (KBr, cm⁻¹): 2941, 1607, 1481, 1308, 1087. \(^1\)H NMR (CDCl₃, 400 MHz): δ 7.57-7.54 (m, 2H), 7.42-7.38 (m, 3H), 7.28-7.21 (m, 3H), 3.86-3.82 (m, 2H), 2.80 (s, J = 7.5 Hz, 2H) ppm. \[^{13}\]C NMR (CDCl₃, 100 MHz): δ 166.2, 138.8, 137.4, 135.3, 130.8, 130.1, 128.4 (two signals: 128.44, 128.36), 127.6, 127.5, 126.6, 47.6, 26.2 ppm. HRMS calcd. for C_{14}H_{14}ClN [M+H]^+ 242.0737; found 242.0728.

1-(3-Nitrophenyl)-3,4-dihydroisoquinoline (3q).

Yield 0.22 g (89%), red oil. IR (film, cm⁻¹): 3294, 1609, 1529, 1349. \(^1\)H NMR (CDCl₃, 500 MHz): δ 8.49-8.48 (m, 1H), 8.32-8.29 (m, 1H), 7.98-7.96 (m, 1H), 7.63-7.60 (m, 1H), 7.45-7.42 (m, 1H), 7.32-7.30 (m, 1H), 7.28-7.26 (m, 1H), 7.19-7.17 (m, 1H), 3.91-3.88 (m, 2H), 2.84 (s, J = 7.2 Hz, 2H) ppm. \[^{13}\]C NMR (CDCl₃, 200 MHz, DMSO-d₆): δ 8.37-8.31 (m, 2H), 8.00 (m, 1H), 7.76 (m, 1H), 7.53-7.26 (m, 3H), 7.18 (m, 1H), 3.80 (m, 2H), 2.78 (m, 2H) ppm. HRMS calcd. for C_{14}H_{14}NO [M+H]^+ 253.0978; found 253.0978.

1-(2-Methoxyphenyl)-3,4-dihydroisoquinoline (3r).

Yield 0.17 g (71%), white crystals (i-Pr_2O). IR (KBr, cm⁻¹): 3396, 3019, 1671, 1613, 1489, 1239, 970, 742. \(^1\)H NMR (CDCl₃, 500 MHz): δ 7.40-7.38 (m, 1H), 7.37-7.34 (m, 1H), 7.33-7.30 (m, 1H), 7.22-7.20 (m, 1H), 7.16-7.13 (m, 1H), 7.04-7.01 (m, 1H), 6.97-6.96 (m, 1H), 6.95-6.93 (m, 1H), 6.67 (s, 3H), 3.90 (bs, 2H), 2.86-2.83 (m, 2H) ppm. \[^{13}\]C NMR (CDCl₃, 400 MHz, CDCl₃): δ 7.42-7.28 (m, 3H), 7.24-7.10 (m, 2H), 7.02 (m, 1H), 6.94 (m, 2H), 3.90 (m, 2H), 3.68 (s, 3H), 2.86 (m, 2H) ppm.] \(^1\)C NMR (CDCl₃, 125 MHz): δ 166.2, 157.2, 137.0, 130.3, 130.2, 130.0, 129.7, 128.8, 127.2, 127.1, 126.6, 120.8, 111.1, 55.5, 47.6, 26.0 ppm. HRMS calcd. for C_{14}H_{14}NO [M+H]^+ 238.1232; found 238.1222.

References