Heck Arylation of Endocyclic Enecarbamates with Diazonium Salts. Improvements and a Concise Enantioselective Synthesis of (-)-Codonopsinine

Elias A. Severino and Carlos Roque D. Correia*

Instituto de Química, Universidade Estadual de Campinas, P. O. Box 6154, Campinas, 13083-970, São Paulo, Brazil

Email:roque@iqm.unicamp.br

Supporting Information:

Spectroscopic data of selected compounds:

(5*S*)-*N*-(Methoxycarbonyl)-5-[(*tert*-Butyldiphenylsilyloxy)methyl]-2-pyrroline (3): TLC: R_f = 0.30 (EtOAc:hexane;1:6). $[\alpha]^{20}_D$ = -74.6 (0.80, hexane). FTIR(neat): 1708, 1450, 1394, 1112 cm^{-1}. ^1H NMR (CCl_4, 300 MHz) (mixture of rotamers): δ 1.03 (s, 9H), 2.74 (bs, 0.9H), 2.79 (bs, 1.1H), 3.46 (bs, 1.3H), 3.63 (bs, 2.5H), 3.80 (bs, 2H), 4.15 (bs, 0.4H), 4.24 (bs, 0.6H), 4.90 (bs, 0.7H), 4.93 (bs, 0.3H), 6.38 (bs, 0.6H), 6.51 (bs, 0.4H), 7.30-7.35 (m, 6H), 7.52-7.63 (m, 4H). ^{13}C NMR (CCl_4) (mixture of rotamers): δ 19.2 (C), 26.8 (CH_3), 32.2 (CH_2), 33.3 (CH_2), 51.9 (CH_3), 57.7 (CH), 58.1 (CH), 63.6 (CH_2), 64.1 (CH_2), 106.4 (CH), 106.8 (CH), 127.8 (CH), 129.8 (CH), 130.7 (CH), 133.7 (C), 135.7 (CH), 135.8 (CH), 152.0 (C). MS *m/z* (rel intensity): 338(100), 213(60), 183(25), 135(5), 105(5). Anal. calcd. for $C_{23}H_{29}NO_3Si$: C, 69.84; H, 7.39; N, 3.54. Found: C, 69.64; H, 7.22; N, 3.48.

(5*S*)-*N*-(Methoxycarbonyl)-5-(Trityloxymethyl)-2-pyrroline (4): Rf 0.27 (Hexane/EtOAc 5:1); $[\alpha]_D^{20}$ -78.4 (c 9.8 in CH_2Cl_2); FTIR (film, NaCl): ν 3055, 3025, 2960, 2865, 1706, 1622, 1599, 1450, 1397, 1147 cm^{-1}; ^1H RMN ($CDCl_3$, 300 MHz): δ 2.61 (s, 0.3H), 2.66 (s, 0.7H), 2.80 (bs, 1H), 3.24 (m, 2H), 3.59 (s, 0.3H), 3.70 (s, 0.7H), 4.24 (bs, 0.5H), 4.32 (bs, 0.5H), 5.04 (s, 1H), 6.50 (s, 0.5H), 6.60 (s, 0.5H), 7.20-7.30 (m, 10H), 7.41-7.44 (m, 5H); HRMS (EI): calcd for $C_{26}H_{25}NO_3$ [M^+] 399.18344, found 399.18356

(*2RS,5S*)-*N*-(Methoxycarbonyl)-5-(Trityloxymethyl)-2-(*p*-Methoxyphenyl)-3-pyrrolines (5a,b): Rf 0.22 (Hexane/EtOAc 3:1); $[\alpha]_D^{20}$ -152 (c 1.1 in CH_2Cl_2); FTIR (film, NaCl): ν 3062, 2959, 2876, 1709, 1611, 1514, 1445, 1372, 1240, 1176, 1035 cm^{-1}; ^1H RMN ($CDCl_3$, 300 MHz) (diastereomers and rotamers): δ 3.30-3.60 (m, 2H), 3.37 (s, 1.5H), 3.40 (s, 1.5H), 3.79 (s, 1.5H), 3.80 (s, 1.5H), 4.80 (m, 0.5H), 4.94 (m, 0.5H), 5.48 (m, 0.5H), 5.58 (m, 0.5H), 5.77 (m, 0.5H), 5.84 (m, 0.5H), 5.98 (m, 1H) 6.84 (d, J = 6.6 Hz 1H), 6.87 (d, J = 6.6 Hz 1H), 7.21-7.35 (m, 10H), 7.44-7.48 (m, 5H).

(*2RS,5S*)-*N*-(Methoxycarbonyl)-5-(hydroxymethyl)-2-(*p*-methoxyphenyl)-3-pyrrolines (7a,b): *Trans isomer* **(*2S,5S*) (7a)**: Rf 0.30 (Hexane/EtOAc 1:3); $[\alpha]_D^{20}$ -272 (c 1.5 in CH_2Cl_2); FTIR (film, NaCl): ν 3433, 2954, 2887, 1684, 1628, 1512, 1454, 1387, 1246 cm^{-1}; ^1H RMN (CCl_4, 300 MHz) (rotamers): δ 3.48 (s, 3H), 3.59 (dd, J = 6.5 and 11.3 Hz, 1H), 3.70 (m, 1H), 3.76 (s, 3H), 4.09 (d, J = 10.2 Hz, 1H), 4.85 (m, 1H), 5.34 (d, J = 5.1 Hz, 1H), 5.69 (m, 2H), 6.74 (d, J = 8.8 Hz, 2H), 7,00 (d, J = 8.8 Hz, 2H); ^{13}C RMN (CCl_4, 75 MHz): δ 52.2, 54.6, 66.4, 68.6, 69.3, 113.9, 126.2, 127.6, 132.1, 133.3, 156.3, 159.3; MS: m/z (rel intens) 59 (5), 77 (5), 103 (5), 115 (5), 130 (7), 145 (5), 156 (5), 158 (17), 159 (5)172 (18), 173 (22), 200 (16), 232 (100), 233 (22), 263 (3); HRMS (EI): calcd for $C_{14}H_{17}NO_4$ $[M^+]$ 263.11576, found 263.11567

C*is* isomer **(*2R,5S*) (7b)**: Rf 0.60 (Hexane/EtOAc 1:3); $[\alpha]_D^{20}$ +113 (c 4.5 in CH_2Cl_2); FTIR (film, NaCl): ν 3419, 2954, 2837, 1697, 1610, 1512, 1452, 1381, 1250 cm^{-1}; ^1H RMN ($CDCl_3$, 500 MHz): δ 3.84 (s, 3H), 3.90 (m, 2H) 3.95 (s, 1H), 4.00 (s, 3H) 4.10 (m, 1H), 5.69 (bs, 0.3H), 5.05 (bs, 0.7H), 5.69 (s, 0.7H), 5.79 (s, 0.3H), 5.95 (bs, 1.4H), 6.08 (bs, 0.6H) 7.05 (d, J = 8 Hz, 2H), 7.39 (d, J = 8 Hz, 2H); HRMS (EI): calcd for $C_{14}H_{17}NO_4$ $[M^+]$ 263.11575, found 263.11552

(*2S,5R*)-*N*-(Methoxycarbonyl)-5-(methyl)-2-(*p*-methoxyphenyl)-3-pyrroline (8): Rf 0.22 (Hexane/EtOAc 3:1); $[\alpha]_D^{20}$ -326 (c 3.6 in CH_2Cl_2); FTIR (film, NaCl): ν 2958, 1701, 1610, 1510, 1448, 1379, 1246, 1174, 1128, 1111, 1036, 829, 710 cm^{-1}; ^1H RMN (CCl_4, 300 MHz) (rotamers): δ 1.36 (d, J = 6.2 Hz, 1.4H), 1.44 (d, J = 6.2 Hz, 1.6 H) 1.58 (s, 3H), 3.43

(s, 1.6H), 3.64 (s, 1.4H), 3.80 (bs, 3H), 4.72 (m, 0.5H), 4.85 (m, 0.5H), 5.40 (m, 0.5H), 5.49 (m, 0.5H), 5.63 (m, 1H), 5.78 (m, 1H) 6.83 (d, J = 8.4 Hz, 0.9H), 6.79 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 8.8 Hz, 1.1 H), 7.19 (d, J = 8.4 Hz, 0.9H); MS: m/z (rel intens): 59 (100), 77 (70), 81 (40), 103 (36), 115 (33), 130 (30), 140 (35), 158 (55) 172 (65), 188 (88), 200 (43), 232 (76), 247 (27); HRMS (EI): calcd for $C_{14}H_{17}NO_3$ [M^+] 247.12084, found 247.12047

(*2R,3R,4S,5R*)-*N*-(Methoxycarbonyl)-3,4-epoxy-5-(methyl)-2-(*p*-methoxyphenyl)-pyrrolidine (9a): Rf 0.31 (Hexane/EtOAc 1:1); mp ; $[\alpha]_D^{20}$ -181 (c 1.6 in CH_2Cl_2); FTIR (film, NaCl): ν 3003, 2954, 2837, 1703, 1612, 1514, 1450, 1363, 1248 cm^{-1}; ^1H RMN ($CDCl_3$, 300 MHz) (rotamers): δ 1.50 (d, J = 5.9 Hz, 1H), 1.58 (d, J = 5.9 Hz, 1H), 3.43 (s, 2H), 3.48 (t, J = 2.9 Hz, 1H), 3.61 (s, 1H), 3.72 (m, 1H), 3.78 (s, 1H), 3.80 (s, 2H), 4.10 (qd, J = 5.9 and 1.5 Hz, 0.3H), 4.17 (qd, J = 5.9 and 1.5 Hz, 0.7H), 4.96 (s, 0.7H), 5.03 (s, 0.3H), 6.86 (d, 8.8 Hz, 2H) 7.07 (d, J = 8.8 Hz, 1.4H), 7.14 (d, J = 8.8 Hz, 1.4H); HRMS (EI): calcd for $C_{14}H_{17}NO_4$ [M^+] 263.11575, found 263.11545

(*2R,3R,4R,5R*)-*N*-(Methoxycarbonyl)-3,4-dihydroxy-5-(methyl)-2-(*p*-methoxyphenyl)-pyrrolidine (10): Rf 0.20 (Hexane/EtOAc 1:2); FTIR (film, NaCl): ν 3411, 2918, 2837, 1674, 1612, 1514, 1456, 1387, 1248 cm^{-1}; ^1H RMN (Pyd_5, 500 MHz) (rotamers): δ 1.74 (d, J = 6.1 Hz, 0.3H), 1.92 (d, J = 6.1 Hz, 0.7H), 3.47 (bs, 3H), 3.59 and 3.60 (bs, 3H), 3.69 (bs, 1H), 4.52 (m, 2H), 4.67 (t, J = 2.5 Hz, 1H), 6.92 (d, J = 8 Hz, 2H), 7.50 (d, J = 8 Hz, 1H), 7.65 (d, J = 8 Hz, 1H); HRMS (EI): calcd for $C_{14}H_{19}NO_3$ [M^+] 281.12632, found 281.12649

(*2R,3R,4R,5R*)-3,4–Dihydroxy-1,5-dimethyl-2-(*p*-methoxyphenyl)-pirrolidine:(-)-Codonopsinine (1): Rf 0.23 (MeOH/$CHCl_3$ 1:4); mp 153-155°C; $[\alpha]_D^{20}$ -7.3 (c 0.15 in MeOH); FTIR (KBr): ν 3384, 2924, 2857, 1615, 1517, 1460, 1258, 1180, 1118, 1051, 1036, 844 cm^{-1}; ^1H RMN (Pyd_5, 500 MHz): 1.30 (d, J = 7 Hz, 3H), 2.20 (s, 3H), 3.65 (s, 3H), 3.70 (qd, J = 7 and 4.4 Hz, 1H), 4.1 (d, J = 6.2 Hz, 1H), 4.40 (t, J = 4.4 Hz, 1H), 4.68 (dd, J = 6.2 and 4.4 Hz, 1H), 6.96 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H); HRMS (EI): calcd for $C_{13}H_{19}NO_3$ [M^+] 237.13649, found 237.13634