Supplementary Material (ESI) for Chemical Communications

Supporting Information

Domino allylic amination/ Sonogashira / heterocyclisation reactions: palladium-catalysed three components synthesis of pyrroles

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General Information

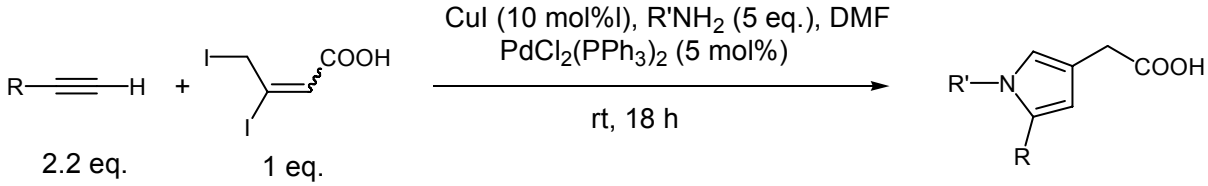
All reactions were carried out under inert atmosphere (Ar or N_2) with dry solvents under anhydrous conditions, unless otherwise noted. All the chemicals were purchased commercially, and used without further purification. Anhydrous THF and diethyl ether were distilled from sodium-benzophenone, and DMF was distilled from calcium hydride. Petroleum ether used was the fraction boiling in the range 40-60 °C.

Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography.

Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated.

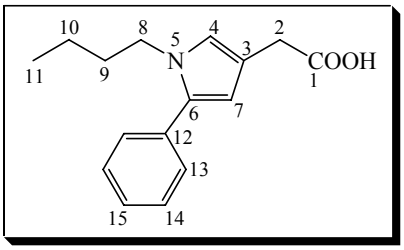
^{1}H NMR spectra were recorded at 200 MHz using $CDCl_3$ as solvent. Findings, reported using the residual solvent proton resonance of $CDCl_3$ (δ_H = 7.27 ppm) as internal reference, were as follows (in order): chemical shift (δ in ppm in relation to Me_4Si), multiplicity (s, d, t, q, m, b for singlet, doublet, triplet, quartet, multiplet, broad) and coupling constants (J in Hz). ^{13}C NMR was recorded at 50 MHz using the $CDCl_3$ solvent peak at δ_C = 77.0 ppm as reference.

General procedure for the synthesis of pyrrol-acetic acid.



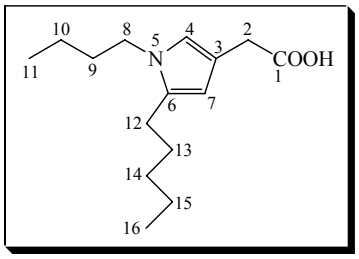
A dry Schlenk tube equipped with a Teflon-coated magnetic stirrer was charged with alkyne (5.5 mmol, 2.2 eq.), amine (12.5 mmol, 5 eq.) in DMF (2 mL) and CuI (0.25 mmol, 10 mol%). Then, the mixture was degassed at -80 °C for 10 min and backfilled with argon and the suspension was stirred for 15 min. At 0 °C, the diiodo acid (2.5 mmol, 1 eq.) was added and finally dichlorobis(triphénylphosphine)palladium (II) (0.0125 mmol, 5 mol%). The mixture was stirred at room temperature for 18 h. The reaction was quenched with saturated aqueous solution of NH_4Cl (20 mL) and extracted with Et_2O (30 mL × 3). The aqueous layer was acidified at 0 °C with 1M HCl solution, extracted with Et_2O (30 mL × 3) and washed with aqueous solution of NaCl (5 mL × 3). The combined organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The material thus obtained was purified by flash chromatography on silica gel to give the desired pyrrol-acetic acid (petroleum ether/Et_2O = 80/20).

2-(1-Butyl-5-phenyl-1*H*-pyrrol-3-yl)acetic acid



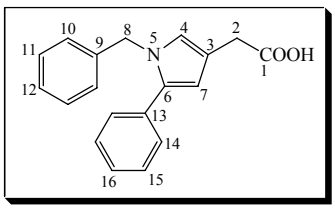
IR: 3400, 1715, 1610; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.43-7.30 (m, $5H_{Ar}$), 6.76 (d, J = 1.9 Hz, H_4), 6.17 (d, J = 1.9 Hz, H_7), 3.92 (t, J = 7.2 Hz, $2H_8$), 3.61 (s, $2H_2$), 1.68 (qt, J = 7.5 Hz, $2H_9$), 1.32-1.21 (m, $2H_{10}$), 0.87 (t, J = 7.2 Hz, $3H_{11}$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.7 (C_1), 135.8 (C_{13}), 133.7 (C_6), 129.6 ($2C_{14}$), 129.0 ($2C_{13}$), 127.5 (C_{15}), 121.5 (C_4), 114.4 (C_3), 110.1 (C_7), 47.8 (C_8), 33.8 (C_2), 32.6 (C_9), 20.8 (C_{10}), 14.2 (C_{11}); MS (EI) *m/z* (%) 213 (M^+, 34), 184 (4), 170 (100), 156 (15). HRMS (ESI) calcd for $C_{12}H_{20}Na_1O_3$ $[M+Na]^+$: 235.1304; found: 235.1300

2-(1-Butyl-5-pentyl-1*H*-pyrrol-3-yl)acetic acid



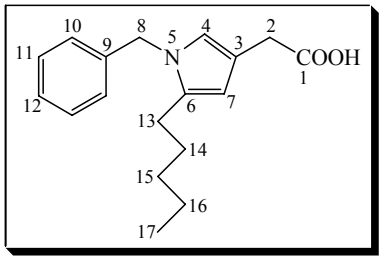
IR: 3405, 2960, 2873, 1709; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.52 (s, H_4), 5.84 (s, H_7), 3.73 (t, J = 7.3 Hz, $2H_8$), 3.49 (s, $2H_2$), 2.48 (t, J = 7.2 Hz, $2H_{12}$), 1.72-0.87 (m, 16H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.0 (C_1), 134.0 (C_6), 118.9 (C_4), 113.6 (C_3), 106.4 (C_7), 46.5 (C_8), 33.9 (C_2), 33.5 (C_{13}), 32.2 (C_9), 28.8 (C_{14}), 26.6 (C_{12}), 23.0 (C_{15}), 20.5 (C_{10}), 14.5 (C_{16}), 14.2 (C_{11}); MS (EI) *m/z* (%) 207 (M^+, 19), 164 (17), 151 (14), 150 (73), 136 (26), 122 (17), 120 (10), 109 (31), 108 (63), 94 (40), 77 (11), 67 (16), 65 (13), 55 (11), 53 (14), 43 (15), 42 (17), 41 (100), 39 (41)

2-(1-Benzyl-5-phenyl-1*H*-pyrrol-3-yl)acetic acid



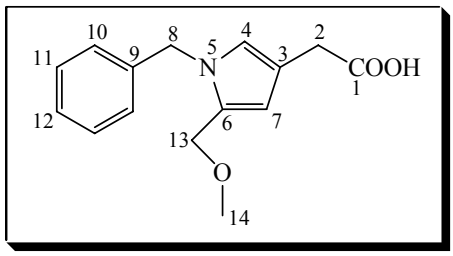
IR: 3030, 1705, 1605, 1513, 1496, 1476, 1453, 1356; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35-7.27 (m, $8H_{Ar}$), 7.04 (dd, J = 7.8 Hz, J = 1.9 Hz, $2H_{10}$), 6.70 (d, J = 1.9 Hz, $1H_4$), 6.25 (d, J = 1.9 Hz, $1H_{7,}$), 5.11 (s, $2H_8$), 3.59 (s, $2H_{2,}$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.8 (C_1), 139.1 (C_9), 135.6 (C_{13}), 133.4 (C_6), 129.3 ($2C_{10}$), 129.1 ($2C_{15}$), 128.9 ($2C_{11}$), 127.8 (C_{16}), 127.5 (C_{12}), 127.0 ($2C_{14}$), 122.6 (C_4), 115.6 (C_3), 110.3 (C_7), 51.1 (C_8), 31.3 (C_2); MS (EI) *m/z* (%) 247 (M^+, 16), 156 (23), 129 (14), 128 (22), 127 (10), 91 (100), 77 (10), 65 (30), 51 (13), 39 (14);

2-(1-Benzyl-5-pentyl-1*H*-pyrrol-3-yl)acetic acid



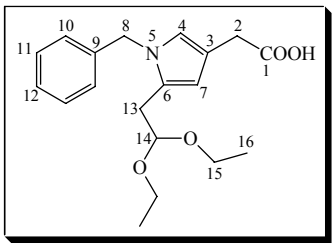
IR: 2929, 2670, 1712, 1606, 1511, 1496, 1455, 1428; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.44-7.31 (m, $3H_{Ar}$), 7.09 (d, J = 6.2 Hz, $2H_{10,}$), 6.62 (s, $1H_{4,}$), 6.01 (s, $1H_7$), 5.05 (s, $2H_8$), 3.58 (s $2H_2$), 2.50 (t, J = 7.3 Hz, $2H_{13}$), 1.69-0.92 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.4 (C_1), 138.9 (C_9), 134.6 (C_6), 129.2 ($2C_{10}$), 127.8 (C_{12}), 126.9 ($2C_{11}$), 120.1 (C_4), 114.3 (C_3), 107.4 (C_7), 50.6 (C_8), 33.6 (C_2), 32.1 (C_{14}), 28.8 (C_{15}), 26.7 (C_{13}), 23.0 (C_{16}), 14.5 (C_{17}); MS (EI) *m/z* (%) 241 (M^+, 12), 185 (12), 184 (36), 91 (100), 65 (25), 41 (22), 39 (16);

2-(1-Benzyl-5-methoxyméthyl-1*H*-pyrrol-3-yl)acetic acid



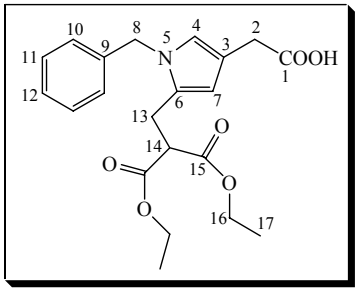
IR: 3060, 2927, 1709, 1652, 1496, 1454, 1355; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33-7.27 (m, $3H_{Ar}$), 7.09 (d, J = 7.4 Hz, $2H_{10}$), 6.63 (s, $H_{4,}$), 6.15 (s, $H_{7,}$), 5.10 (s, $2H_8$), 4.28 (s, $2H_{13}$), 3.49 (s, $2H_2$), 3.26 (s, $3H_{14}$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.7 (C_1), 138.7 (C_{9+6}), 129.2 ($2C_{10}$), 127.9 (C_{12}), 127.3 ($2C_{11}$), 122.6 (C_4), 114.5 (C_3), 112.1 (C_7), 66.3 (C_{13}), 57.5 (C_{14}), 50.9 (C_8), 33.4 (C_2); MS (EI) *m/z* (%) 171 (M^+, 26), 91 (100), 65 (30), 53 (10), 51 (12), 39 (24).

2-(1-Benzyl-5-(2,2-diethoxy-éthyl)-1*H*-pyrrol-3-yl)acetic acid



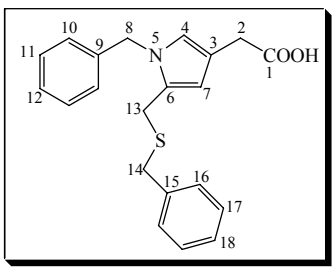
IR: 3200, 3030, 2975, 2930, 1708, 1606, 1497, 1454, 1373; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37-7.24 ($3H_{Ar}$, m), 7.02 (d, J = 8.0 Hz, $2H_{10}$), 6.56 (d, J = 1.9 Hz, H_4), 6.03 (d, J = 1.9 Hz, H_7), 5.08 (s, $2H_8$), 4.53 (t, J = 5.6 Hz, H_{14}), 3.51 (s, $2H_2$), 3.66-3.37 (m, $4H_{15}$), 2.79 (d, J = 5.5 Hz, $2H_{13}$), 1.16 (t, J = 7.1 Hz, $6H_{16}$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.0 (C_1), 138.9 (C_9), 129.1 ($2C_{10}$), 127.7 (C_{12}), 127.0 ($2C_{11}$), 120.6 (C_4), 114.4 (C_3), 109.5 (C_7), 103.5 (C_{14}), 62.6 ($2C_{15}$), 50.9 (C_8), 33.5 (C_2), 32.1 (C_{13}), 15.6 ($2C_{16}$); MS (EI) *m/z* (%) 287 (M^+, 4), 103 (71), 91 (60), 75 (68), 65 (16), 47 (100).

2-(1-Benzyl-4-carboxymethyl-1*H*-pyrrol-2-ylmethyl)malonic acid diethyl ester



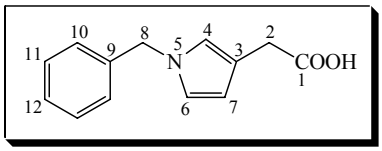
IR: 3031, 2983, 2938, 1730, 1497, 1454, 1370, 1224, 1155; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36-7.26 (m, $3H_{Ar}$), 7.03 (d, J = 6.3 Hz, $2H_{10}$), 6.57 (s, H_4), 5.94 (s, H_7), 5.04 (s, $2H_8$), 4.17 (q, J = 7.1 Hz, $4H_{16}$), 3.56 (t, J = 7.7 Hz, H_{14}), 3.47 (s, $2H_2$), 3.09 (d, J = 7.7 Hz, $2H_{13}$), 1.23 (t, J = 7.2 Hz, $6H_{17}$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.9 (C_1), 169.2 ($2C_{15}$), 138.3 (C_9), 129.6 (C_6), 129.2 ($2C_{10}$), 127.9 (C_{12}), 126.9 ($2C_{11}$), 121.0 (C_4), 114.4 (C_3), 108.6 (C_7), 62.0 ($2C_{16}$), 52.0 (C_{14}), 50.7 (C_8), 33.3 (C_2), 25.8 (C_{13}), 14.4 ($2C_{17}$); MS (EI) *m/z* (%) 343 (M^+, 11), 185 (10), 184 (64), 91 (100), 65 (12).

2-(1-Benzyl-5-phenylsulfanylmethyl-1*H*-pyrrol-3-yl)acetic acid



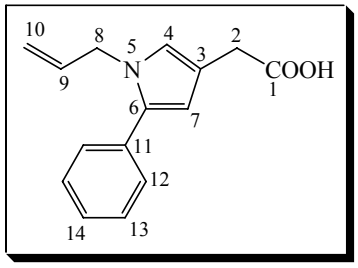
IR: 3200, 3061, 1708, 1495, 1454, 1265; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41-7.37 (m, $8H_{Ar}$), 7.12 (d, J = 7.6 Hz, $2H_{10}$), 6.71 (d, J = 1.3 Hz, H_4), 6.19 (d, J = 1.3 Hz, H_7), 5.16 (s, $2H_8$), 3.75 (s, $2H_{13}$), 3.63 (s, $2H_{14}$), 3.58 (s, $2H_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.2 (C_1), 138.9 ($C1_5$), 138.5 (C_9), 129.6 ($2C_{17}$), 129.3 ($2C_{10}$), 129.0 ($2C_{11}$), 128.1 (C_6), 128.0 (C_{12}), 127.5 (C_{18}), 127.3 ($2C_{17}$), 122.2 (C_4), 114.2 (C_3), 111.5 (C_7), 50.8 (C_8), 36.0 (C_{14}), 33.5 (C_2), 27.4 (C_{13}); MS (EI) *m/z* (%) 307 (M^+, 3), 184 (53), 91 (100), 65 (20).

2-(1-Benzyl-1*H*-pyrrol-3-yl)acetic acid



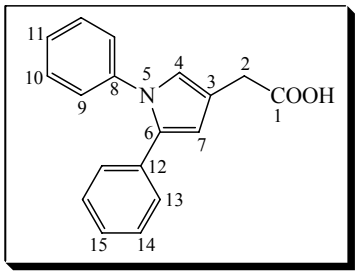
IR: 3294, 3061, 3031, 2928, 1705, 1498, 1454, 1385, 1357, 1228; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39-7.26 ($3H_{Ar}$, m), 7.14 (dd, J = 7.8 Hz, J = 2.2 Hz, $2H_{10}$), 6.64 (d, J = 2.3 Hz, H_4 + H_6), 6.14 (t, J = 2.3 Hz, H_7), 5.03 (s, $2H_8$), 3.54 (s, $2H_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.7 (C_1), 138.4 (C_9), 129.2 ($2C_{10}$), 128.2 (C_{12}), 127.6 ($2C_{11}$), 121.9 (C_6), 120.6 (C_4), 115.8 (C_3), 109.9 (C_7), 53.8 (C_8), 33.5 (C_2); MS (EI) *m/z* (%) 215 (M^+, 59), 170 (52), 91 (100), 65 (14).

2-(1-Allyl-5-phenyl-1*H*-pyrrol-3-yl)acetic acid



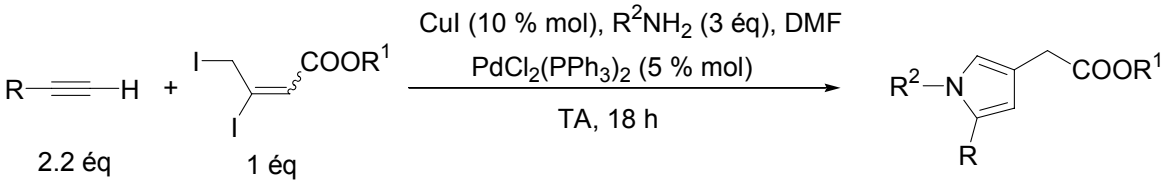
IR: 3067, 2961, 2927, 1709, 1604, 1513, 1474, 1447, 1408, 1261; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41-7.27 (m, $5H_{Ar}$), 6.73 (d, J = 1.9 Hz, H_4), 6.21 (d, H_7, J = 1.9 Hz), 5.98 (ddt, J = 17 Hz, J = 10.3 Hz, J = 5.1 Hz, H_9), 5.22 (dd, J = 10.3 Hz, J = 1.4 Hz, $1H_{10}$), 5.09 (dd, J = 17 Hz, J = 1.4 Hz, $1H_{10}$), 4.51 (dt, J = 5.1 Hz, J = 1.6 Hz, $2H_{8,}$), 3.59 (s, $2H_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.2 (C_1), 135.2 (C_9), 133.4 (C_6 et C_{11}), 129.2 ($2C_{13}$), 128.8 ($2C_{12}$), 127.4 (C_{14}), 121.7 (C_4), 117.6 (C_{10}), 115.2 (C_3), 110.0 (C_7), 49.9 (C_8), 33.4 (C_2); MS (EI) *m/z* (%) 241 (M^+, 84), 197 (15), 196 (100), 182 (36), 168 (12), 167 (12), 155 (20), 154 (25), 144 (10), 129 (13), 128 (44), 127 (28), 115 (14), 102 (19), 91 (14), 77 (30), 51 (22), 45 (19), 41 (80), 39 (56).

2-(1,5-Diphenyl-1*H*-pyrrol-3-yl)acetic acid



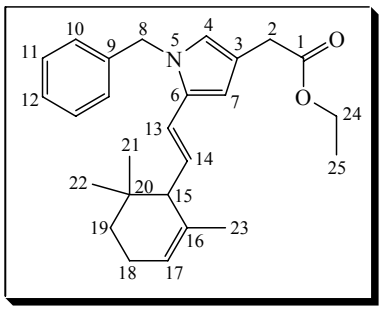
IR: 3052, 2925, 2674, 1704, 1628, 1599, 1500, 1434, 1407, 1372, 1308, 1265, 1135; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.11-7.48 (m, $10H_{Ar}$), 6.93 (d, J = 1.9Hz, H_4), 6.44 (d, J = 1.9 Hz, H_7), 3.64 (s, $2H_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.3 (C_1), 140.7 (C_8), 134.4 (C_6 or C_{12}), 133.1 (C_6 or C_{12}), 129.4 ($2C_{10}$), 128.7 ($2C_{14}$), 128.5 ($2C_{13}$), 127.0 (C_{15}), 126.8 (C_{11}), 126.1 ($2C_9$), 123.7 (C_4), 116.3 (C_3), 112.1 (C_7),33.2 (C_2); MS (EI) *m/z* (%) 277 (M^+, 77), 233 (25), 232 (100), 128 (22), 105 (35), 93 (42), 77 (81), 51 (38), 44 (59), 43 (11), 40 (38), 39 (15).

General procedure for the synthesis of pyrrol-acetic ester.



A dry Schlenk tube equipped with a Teflon-coated magnetic stirrer was charged with alkyne (5.5 mmol, 2.2 eq.), amine (12.5 mmol, 5 eq.) in DMF (2 mL) and CuI (0.25 mmol, 10 mol%). Then, the mixture was degassed at -80 °C for 10 min and backfilled with argon and the suspension was stirred for 15 min. At 0 °C, the diiodo acid (2.5 mmol, 1 eq.) was added and finally dichlorobis(triphénylphosphine)palladium (II) (0.0125 mmol, 5 mol%). The mixture was stirred at room temperature for 18 h. The reaction was quenched with saturated aqueous solution of NH_4Cl (20 mL) and extracted with Et_2O (30 mL × 3). The combined organic layers were washed with aqueous solution of NaCl (5 mL × 3), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The material thus obtained was purified by flash chromatography on silica gel to give the desired pyrrol-acetic ester (petroleum ether/Et_2O = 95/5).

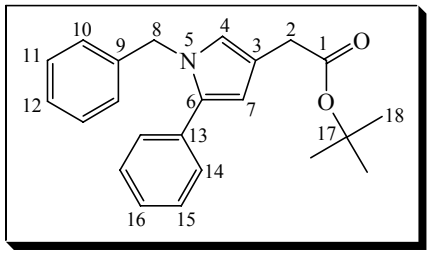
{1-Benzyl-5-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-vinyl]-1*H*-pyrrol-3-yl}-acetic acid ethyl ester



Rdt :

IR: 2960, 2929, 2871, 1713, 1497, 1455, 1435, 1397, 1346, 1220, 1185; ^{1}H NMR (200 MHz, $CDCl_3$) δ ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.9 (C_1), 138.6 (C_{16}), 134.5 (C_9), 132.5 (C_6), 130.9 (C_{14}), 129.1 ($2C_{10}$), 127.7 (C_{13}), 126.9 ($2C_{11}$), 121.3 (C_{12}), 121.1 (C_{17}), 120.3 (C_4), 115.9 (C_3), 107.1 (C_7), 61.0 (C_{24}), 55.3 (C_{15}), 51.0 (C_8), 33.5 (C_2 or C_{19}), 32.9 (C_{20}), 31.9 (C_2 or C_{19}), 27.9 (C_{21} or C_{22}), 27.3 (C_{21} or C_{22}), 23.5 (C_{18}), 23.2 (C_{23}), 14.6 (C_{25}); MS (EI) *m/z* (%) (M^+,.

***tert*-Butyl 2-(1-Benzyl-5-phenyl-1*H*-pyrrol-3-yl)acetate**



Rdt :

IR: 3063, 2976, 2930, 1732, 1604, 1512, 1496, 1476, 1454, 1392, 1368, 1259, 1145; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37-7.23 (m, $8H_{Ar}$), 7.06 (dd, J = 8.0 Hz, J = 2.0 Hz, $2H_{10}$), 6.71 (d, J = 1.9 Hz, H_4), 6.27 (d, J = 1.9 Hz, H_7), 5.13 (s, $2H_8$), 3.47 (s, $2H_2$), 1.51 (s, $9H_{18}$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.2 (C_1), 139.3 (C_9), 135.3 (C_{13}), 133.6 (C_6), 129.2 ($2C_{10}$), 129.1 ($2C_{15}$), 128.8 ($2C_{11}$), 127.7 (C_{16}), 127.3 (C_{12}), 126.9 ($2C_{14}$), 122.0 (C_4), 116.9 (C_3), 110.2 (C_7), 80.7 (C_{17}), 51.0 (C_8), 34.8 (C_2), 28.6 ($3C_{18}$); MS (EI) *m/z* (%) 347 (M^+, 29), 291 (33), 246 (44), 149 (20), 91 (100), 65 (10), 57 (31), 41 (19).