Supporting Information

Fast, Mild, Eco-Friendly Synthesis of Polyfunctionalized Pyrroles from β-Nitroacrylates and β-Enaminones

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Experimental Section. ^{1}H NMR were recorded at 400 MHz. ^{13}C NMR were recorded at 100 MHz. GLC analyses were performed on a capillary column of fused silica (0.32 mm×25 m), stationary phase SE54. Mass spectra were performed on a GC/MS system by means of the EI technique (70 eV). Infrared spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer. Microanalyses were performed with a CHNS-O analyzer Model EA 1108 from Fisons Instruments.

General Procedure for the synthesis of compounds 3. The β-nitroacrylate **1** (1 mmol) and β-enamione **2** (1 mmol) were slowly mixed at 0°C (ice/water bath). The reaction was stirred for 15 minutes at the same temperature, after that, the bath was removed, and temperature was left up increase to room temperature, then reaction was stirred for the needed time (monitored by TLC, see Table 1). After the reaction was completed, the crude product **3** was directly purified by flash chromatography column (hexanes : EtOAc = 80:20).

Large scale synthesis of compound 3aa
To a stirred β-nitroacrylate **1a** (10 mmol) maintained a 0°C (ice/water bath), the β-enaminone **2** (10 mmol) was slowly added over 30 min, then the reaction was stirred at room temperature for 3.5 hours. After the reaction was completed (TLC), the crude product **3aa** was subjected to the *way a* or the *way b*.
Way a: the product was directly purified by flash chromatography column, using 25g of Silica (60Å, 40-63μm) and 180 ml of eluent mixture (cyclohexane : EtOAc = 95 : 5). The eluate was continuously monitored by TLC and, the eluent mixture was recovered by distillation (40°C/135torr) and reused. The pure product **3aa** was obtained in 93% yield.
Way b: 3.5 mL (~3g) of EtOAc and 2g of dry $MgSO_4$ were added to the crude **3aa**, then the mixture was stirred 15 minutes and filtered through a pad of florisil® (1.5g, 100-200mesh) which was washed with fresh EtOAc (12 ml, ~10.5g). The product **3aa** was obtained in 98% yield (GC purity ≥ 94%).

3aa. Yield 90%. Pale yellow oil. IR (cm^{-1}, neat) ν: 1095, 1177, 1212, 1432, 1536, 1654, 1699. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (t, 3H, *J* = 6.8 Hz), 1.16 (t, 3H, *J* = 7.7 Hz), 1.26-1.37 (m, 10H), 1.54-1.66 (m, 2H), 2.36 (s, 3H), 2.76 (q, 2H, *J* = 7.7 Hz), 3.69-3.75 (m, 2H), 4.20-4.28 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.1, 14.1, 14.5, 15.0, 18.7, 22.5, 29.2, 30.9, 43.9, 60.2, 60.3, 111.7, 112.7, 132.7, 138.9, 165.8, 166.1. EI (MS): *m/z* 323[M^{+}], 278, 248(100), 234, 220, 175, 43, 29. Anal. Calcd. for $C_{18}H_{29}NO_4$ (323.43): C, 66.84; H, 9.04; N, 4.43. Found: C, 66.90; H, 9.08; N, 4.40.

3ba. Yield 88%. Pale yellow oil. IR (cm^{-1}, neat) ν: 1097, 1173, 1215, 1432, 1538, 1652, 1701. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (t, 3H, *J* = 6.8 Hz), 1.16 (t, 3H, *J* = 7.7 Hz), 1.27-1.39 (m, 7H), 1.55-1.66 (m, 2H), 2.36 (s, 3H), 2.76 (q, 2H, *J* = 7.7 Hz), 3.70-3.76 (m, 2H), 3.77 (s, 3H), 4.21-4.28 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.1, 14.1, 14.5, 15.0, 18.6, 22.5, 29.1, 30.8, 43.9, 51.4, 60.2, 111.4, 112.6, 132.9, 139.1, 166.0, 166.2. EI (MS): *m/z* 309[M^{+}], 294, 278, 264, 248(100), 234, 220, 206, 175, 162, 43, 29. Anal. Calcd. for $C_{17}H_{27}NO_4$ (309.19): C, 65.99; H, 8.80; N, 4.53. Found: C, 66.04; H, 8.86; N, 4.49.

3ca. Yield 84%. Pale yellow oil. IR (cm^{-1}, neat) ν: 1044, 1072, 1174, 1213, 1438, 1535, 1654, 1702. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.84-0.93 (m, 6H), 1.24-1.40 (m, 14H), 1.44-1.66 (m, 4H), 2.36 (s, 3H), 2.68-2.75 (m, 2H), 3.67-3.75 (m, 2H), 4.20-4.28 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.2, 14.1, 14.2, 14.5, 22.5, 22.6, 25.3, 29.2, 30.3, 30.8, 32.0, 43.9, 60.2, 60.3, 112.1, 112.7, 132.8, 137.6, 165.9, 166.1. EI (MS): *m/z* 365[M^{+}], 320, 308, 292, 276, 248(100), 234, 220, 164, 43, 29. Anal. Calcd. for $C_{21}H_{35}NO_4$ (365.51): C, 69.01; H, 9.65; N, 3.83. Found: C, 69.10; H, 9.72; N, 3.79.

3da. (diastereomeric mixture 70:30). Yield 86%. Yellow oil. IR (cm^{-1}, neat) ν: 1041, 1074, 1157, 1173, 1212, 1439, 1538, 1650, 1703. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87-0.93 (m, 3H), 1.13 (d, 2.1H, J = 6.4 Hz), 1.23-1.40 (m, 10.9H), 1.44-1.90 (m, 10H), 2.36 (s, 3H), 2.75-2.88 (m, 1.3H), 2.90-3.01 (m, 0.7H), 3.44-3.54 (m, 1H), 3.68-3.98 (m, 4H), 4.19-4.29 (m, 4H), 4.62-4.66 (m, 0.3H), 4.67-4.72 (m, 0.7H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.1, 14.1, 14.2, 14.5, 14.6, 19.2, 20.3, 20.4, 21.6, 21.7, 22.5, 22.6, 25.7, 25.8, 29.2, 30.8, 30.9, 31.5, 31.6, 37.3, 38.1, 43.9, 44.1, 60.1, 60.2, 60.3, 60.4, 63.1, 63.2, 70.8, 74.4, 96.1, 99.5, 111.9, 112.0, 112.7, 112.8, 132.7, 133.1, 137.4, 137.7, 165.7, 165.8, 166.1, 166.2. EI (MS): *m/z* 367, 321, 308, 276(100), 248, 236, 164, 85, 55, 43, 41, 29. Anal. Calcd. for $C_{25}H_{41}NO_6$ (451.60): C, 66.49; H, 9.15; N, 3.10. Found: C, 66.55; H, 9.22; N, 3.07.

3eb. Yield 89%. Yellow oil. IR (cm^{-1}, neat) ν: 730, 1080, 1175, 1213, 1290, 1384, 1435, 1539, 1655, 1702. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.82 (t, 3H, *J* = 7.3 Hz), 1.14-1.46 (m, 10H), 2.27 (s, 3H), 2.66-2.73 (m, 2H), 4.27 (q, 4H, *J* = 7.3 Hz), 5.05 (s, 2H), 6.89 (d, 2H, *J* = 7.3 Hz), 7.21-7.36 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.2, 14.0, 14.5, 22.7, 25.1, 32.5, 47.1, 60.3, 60.4, 112.8, 113.1, 125.8, 127.9, 129.2, 133.6, 136.7, 138.2, 165.8, 166.0. EI (MS): *m/z* 371[M^+], 325, 296, 279, 91(100), 65, 43, 29. Anal. Calcd. for $C_{22}H_{29}NO_4$ (371.47): C, 71.13; H, 7.87; N, 3.77. Found: C, 71.04; H, 7.78; N, 3.81.

3fb. Yield 78%. Yellow viscous oil. IR (cm^{-1}, neat) ν: 699, 731, 1086, 1180, 1216, 1292, 1384, 1435, 1538, 1602, 1651, 1698, 3028, 3063. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30-1.38 (m, 6H), 2.28 (s, 3H), 2.68-2.75 (m, 2H), 2.95-3.02 (m, 2H), 4.25-4.33 (m, 4H), 4.84 (s, 2H), 6.88 (d, 2H, *J* = 7.3 Hz), 7.05 (d, 2H, *J* = 8.1 Hz), 7.26-7.35 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.2, 14.5, 14.6, 27.9, 36.8, 46.9, 60.4, 60.5, 112.8, 113.4, 125.8, 126.4, 127.9, 128.7, 128.8, 129.3, 133.5, 136.6, 137.5, 141.3, 165.6, 166.1. EI (MS): *m/z* 374, 328, 282, 254, 91(100), 65, 43, 29. Anal. Calcd. for $C_{26}H_{29}NO_4$ (419.51): C, 74.44; H, 6.97; N, 3.34. Found: C, 74.53; H, 7.02; N, 3.30.

3gb. Yield 76%. Yellow oil. IR (cm^{-1}, neat) ν: 730, 1046, 1089, 1177, 1217, 1358, 1421, 1441, 1544, 1606, 1698, 3030, 3064. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.32 (t, 3H, *J* = 7.3 Hz), 2.31 (s, 3H), 2.32 (s, 3H), 3.80 (s, 3H), 4.27 (q, 2H, *J* = 7.3 Hz), 5.04 (s, 2H), 6.90 (d, 2H, *J* = 7.7 Hz), 7.22-7.34 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.1, 14.6, 47.2, 51.6, 60.4, 112.6, 112.8, 125.8, 127.9, 129.2, 133.9, 134.0, 136.2, 165.9, 166.4. EI (MS): *m/z* 315[M^+], 283, 269, 237, 91(100), 65, 51, 39, 29. Anal. Calcd. for $C_{18}H_{21}NO_4$ (315.36): C, 68.55; H, 6.71; N, 4.44. Found: C, 68.64; H, 6.78; N, 4.39.

3hb. Yield 70%. Yellow oil. IR (cm^{-1}, neat) ν: 733, 751, 1083, 1175, 1212, 1240, 1384, 1441, 1537, 1652, 1700. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.29-1.36 (m, 6H), 1.85-1.96 (m, 2H), 2.29 (s, 3H), 2.83-2.91 (m, 2H), 3.50 (t, 2H, *J* = 6.4 Hz), 4.23-4.32 (m, 4H), 5.09 (s, 2H), 6.90 (d, 2H, *J* = 7.3 Hz), 7.22-7.38 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.1, 14.5, 22.8, 32.9, 44.7, 47.1, 60.4, 60.5, 113.1, 113.4, 125.7, 127.9, 129.2, 133.6, 136.4, 136.5, 165.8, 165.9. EI (MS): *m/z* 393[M+2$^+$], 391[M^+], 345, 310, 296, 282, 254, 91(100), 65. Anal. Calcd. for $C_{21}H_{26}ClNO_4$ (391.89): C, 64.36; H, 6.69; N, 3.57. Found: C, 64.29; H, 6.63; N, 3.60.

3gc. Yield 91%. Yellow oil. IR (cm^{-1}, neat) ν: 737, 1082, 1176, 1214, 1398, 1441, 1538, 1645, 1698. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.93 (t, 3H, *J* = 7.3 Hz), 1.31 (t, 3H, *J* = 7.3 Hz), 1.48-1.59 (m, 2H), 2.32 (s, 3H), 2.65-2.72 (m, 2H), 3.78 (s, 3H), 4.25 (q, 2H, *J* = 7.3 Hz), 4.38-4.43 (m, 2H), 4.75 (d, 1H, *J* = 17.1 Hz), 5.16 (d, 1H, *J* = 10.3 Hz), 5.78-5.91 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.9, 14.1, 14.5, 23.7, 27.1, 45.8, 51.5, 60.2, 112.4, 112.5, 116.9, 132.7, 133.6, 138.0, 165.7, 166.5. EI (MS): *m/z* 293[M^+], 264, 248, 232, 219, 215, 204(100), 187, 161, 132, 91, 77, 65, 51, 41, 29. Anal. Calcd. for $C_{16}H_{23}NO_4$ (293.36): C, 65.51; H, 7.90; N, 4.77. Found: C, 65.59; H, 7.95; N, 4.73.

3cd. Yield 60%. Yellow oil. IR (cm^{-1}, neat) ν: 702, 1085, 1213, 1247, 1279, 1382, 1420, 1440, 1538, 1598, 1705. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.73 (t, 3H, *J* = 6.8 Hz), 1.02-1.15 (m, 4H), 1.24-1.36 (m, 2H), 1.32 (t, 3H, *J* = 7.3 Hz), 2.09 (s, 3H), 2.48-2.56 (m, 2H), 3.81 (s, 3H), 4.28 (q, 2H, J = 7.3 Hz), 7.13-7.19 (m, 2H), 7.45-7.53 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.0, 14.0, 14.6, 22.2, 25.5, 29.7, 31.6, 51.6, 60.4, 112.5, 112.6, 128.6, 129.4, 129.7, 134.5, 137.0, 139.2, 165.8, 166.4. EI (MS): *m/z* 357[M^+], 325, 311, 300, 268, 240, 228, 168, 118(100), 77, 51, 41, 29. Anal. Calcd. for $C_{21}H_{27}NO_4$ (357.44): C, 70.56; H, 7.61; N, 3.92. Found: C, 70.64; H, 7,67; N, 3.89.

3id. Yield 65%. Yellow oil. IR (cm^{-1}, neat) ν: 702, 1084, 1215, 1247, 1278, 1382, 1440, 1537, 1599, 1698. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.72 (t, 3H, J = 7.3 Hz), 0.95 (t, 3H, J = 7.3 Hz), 1.27-1.49 (m, 4H), 1.63-1.73 (m, 2H), 2.09 (s, 3H), 2.48-2.55 (m, 2H), 3.81 (s, 3H), 4.23 (t, 2H, J = 6.8 Hz), 7.14-7.20 (m, 2H), 7.46-7.53 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.0, 14.0, 14.1, 19.5, 23.4, 27.6, 31.1, 51.7, 64.4, 112.6, 112.7, 128.6, 129.4, 129.7, 134.4, 137.0, 139.0, 165.9, 166.5. EI (MS): *m/z* 357[M^+], 328, 283, 268, 251, 240(100), 223, 196, 168, 154, 118, 104, 77, 51, 41. Anal. Calcd. for $C_{21}H_{27}NO_4$ (357.44): C, 70.56; H, 7.61; N, 3.92. Found: C, 70.62; H, 7.66; N, 3.94.

3ie. Yield 70%. White solid, m.p. = 65-67°C. IR (cm^{-1}, nujol) ν: 1040, 1073, 1174, 1211, 1441, 1536, 1653, 1699. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.21 (t, 6H, J = 7.3 Hz), 2.21 (s, 6H), 3.23 (s, 3H), 4.14 (q, 4H, J = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.0, 14.4, 30.4, 60.0, 112.0, 133.5, 165.8. EI (MS): *m/z* 253[M+], 207, 180, 135, 107, 56(100), 29. Anal. Calcd. for $C_{13}H_{19}NO_4$ (253.29): C, 61.64; H, 7.56; N, 5.53. Found: C, 61.71; H, 7.60; N, 5.48.

3if. Yield 66%. Yellow oil. IR (cm^{-1}, neat) ν: 787, 1149, 1251, 1337, 1413, 1525, 1693. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.91 (t, 3H, J = 7.7 Hz), 0.96 (t, 3H, J = 7.3 Hz), 1.09 (t, 3H, J = 7.3 Hz), 1.12 (t, 3H, J = 7.7 Hz), 1.32-1.43 (m, 2H), 1.48-1.69 (m, 4H), 2.60 (q, 2H, J = 7.3 Hz), 2.67 (q, 2H, J = 7.3 Hz), 2.78- 2.85 (m, 2H), 3.43 (s, 3H), 4.16 (t, 2H, J = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.1, 13.9, 14.2, 14.7, 18.5, 19.5, 23.1, 27.4, 30.3, 31.0, 37.3, 64.0, 110.3, 122.7, 136.1, 139.5, 165.5, 203.8. EI (MS): *m/z* 307[M^+], 278, 234, 222(100), 204, 176, 120, 29. Anal. Calcd. for $C_{18}H_{29}NO_3$ (307.43): C, 70.32; H, 9.51; N, 4.56. Found: C, 70.40; H, 9.59; N, 4.52.

3lg Yield 78%. Yellow oil. IR (cm^{-1}, neat) ν: 676, 724, 925, 1103, 1220, 1384, 1413, 1538, 1597, 1695, 3059. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.69 (t, 3H, J = 6.8 Hz), 2.24 (s, 3H), 2.48 (s, 3H), 3.44 (s, 3H), 3.66 (q, 2H, J = 6.8 Hz), 7.35 (t, 2H, J = 7.8 Hz), 7.40-7.47 (m, 1H), 7.77 (d, 2H, J = 7.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.0, 11.2, 13.6, 30.6, 59.6, 111.8, 120.4, 128.3, 129.2, 132.1, 132.2, 135.3, 140.5, 165.1, 190.0. EI (MS): *m/z* 285[M^+], 284, 239(100), 238, 224, 180, 168, 77, 56, 29. Anal. Calcd. for $C_{17}H_{19}NO_3$ (285.34): C, 71.56; H, 6.71; N, 4.91. Found: C, 71.63; H, 6.75; N, 4.88.

3gd. Yield 85%. White solid, m.p. = 85-87°C (lit.[1] 86-87°C). IR (cm^{-1}, nujol) ν: 703, 745, 791, 1071, 1092, 1218, 1282, 1355, 1384, 1442, 1544, 1599, 1711. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.13 (s, 6H), 3.83 (s, 6H), 7.12-7.18 (m, 2H), 7.44-7.54 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.1, 51.7, 112.6, 128.3, 129.4, 129.9, 134.7, 137.0, 166.3. EI (MS): *m/z* 287[M+], 255, 226, 197, 169, 118, 77(100), 51, 39. Anal. Calcd. for $C_{16}H_{17}NO_4$ (287.31): C, 66.89; H, 5.96; N, 4.88. Found: C, 66.95; H, 5.99; N, 4.84.

1 W. K. Anderson, P. F. Corey, *J. Med. Chem.*, 1977, **20**, 1691.