Supporting Information

New Three Component Reaction: Novel Formation of Seven-Membered Ring by the Unexpected Reaction at the γ -Position of the β -Keto Ester

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Preparation and Physical data of compound 3a-3n

Typical procedure: Ethylenediamine (1.0 equiv.), β -keto ester (1.0 equiv.) and *p*-TsOH $\square$ H₂O (0.1 equiv.) were added to a solution of an aldehyde (1.0 equiv.) in DCE (0.1 M) at rt under N₂. The reaction mixture was heated under reflux for 20 h, cooled to RT, and quenched by sat. aq. NaHCO₃. The mixture was extracted with CH₂Cl₂. The organic layer was dried over Na₂SO₄ and evaporated in vacuo. The residue was purified by SiO₂ column chromatography to give the product in the yield shown in the Tables.

Compound 3a

Colorless solid; m.p. 108 °C; ¹H NMR (300 MHz, CDCl₃): δ = 8.91 (br s, 1H), 7.38-7.25 (m, 5H), 4.47 (s, 1H), 3.76 (d, *J* = 9.6 Hz, 1H), 3.64 (s, 3H), 3.64-3.55 (m, 1H), 3.45-3.36 (m, 1H), 3.17 (dd, *J* = 12.3, 4.8 Hz, 1H), 2.99-2.83 (m, 2H), 2.35 (dd, *J* = 14.4, 0.8 Hz, 1H), 1.95 (br s, 1H); ¹³C NMR (67.8 MHz, CDCl₃): δ = 170.5, 165.2, 144.7, 128.4, 127.3, 126.0, 81.8, 62.4, 50.6, 49.9, 46.2, 45.8; IR (KBr): 3308, 2945, 1655, 1604, 1504, 1303, 1234, 1173 cm⁻¹; HRMS (FAB): calcd for C₁₄H₁₉N₂O₂ [*M* + H]⁺: 247.1447, found 247.1454; *Anal.* Calcd for C₁₄H₁₈N₂O₂: C, 68.27; H, 7.37; N, 11.37. found C, 68.27; H, 7.35; N, 11.36.

Compound 3b

Colorless solid; m.p. 127- 129 °C; ¹H NMR (270 MHz, CDCl₃): δ = 8.90 (br s, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 4.45 (s, 1H), 3.79 (s, 3H), 3.74-3.52 (m, 2H), 3.63 (s, 3H), 3.43-3.36 (m, 1H), 3.15 (dd, *J* = 13.0, 4.9 Hz, 1H), 2.96-2.86 (m, 2H), 2.32 (d, *J* = 14.6 Hz, 1H), 1.99 (br s, 1H); ¹³C NMR (67.8 MHz, CDCl₃): δ = 170.7, 165.4, 158.8, 137.2, 127.2, 113.9, 81.9, 61.9, 55.2, 50.7, 50.0, 46.3, 46.1; IR (KBr): 3321, 2949, 2837, 2252, 1654, 1609, 1508, 1255, 1176 cm⁻¹; HRMS (FAB): calcd for C₁₅H₂₁N₂O₃ [*M* + H]⁺: 277.1552, found 277.1561; *Anal.* Calcd for C₁₅H₂₀N₂O₃: C, 65.20; H, 7.30; N, 10.14. found C, 65.07; H, 7.22; N, 10.03.

Compound 3c

Colorless solid; m.p. 129 °C; ¹H NMR (300 MHz, CDCl₃): δ = 8.90 (br s, 1H), 7.32-7.30 (s, 4H), 4.46 (s, 1H), 3.74 (d, *J* = 9.6 Hz, 1H), 3.64 (s, 3H), 3.64-3.53 (m, 1H), 3.45-3.37 (m, 1H), 3.17 (dd, *J* = 13.5, 4.8 Hz, 1H), 2.93-2.82 (m, 2H), 2.29 (dd, *J* = 14.4, 0.6 Hz, 1H), 1.87 (br s, 1H); ¹³C NMR (67.8 MHz, CDCl₃): δ = 170.7, 164.9, 143.3, 133.1, 128.7, 127.6, 82.1, 61.9, 50.6, 5.01, 46.2, 46.0; IR (KBr): 3306, 2947, 2837, 2253, 1655, 1603, 1491, 1300, 1250, 1173 cm⁻¹; HRMS (FAB): calcd for C₁₄H₁₈ClN₂O₂ [*M* + H]⁺: 281.1057, found 281.1075; *Anal.* Calcd for C₁₄H₁₇ClN₂O₃: C, 59.89; H, 6.10; N, 9.98. Cl, 12.63. found C, 59.90; H, 6.08; N, 9.94. Cl, 12.46.

Compound 3d

Colorless solid; m.p. 134- 135 °C; ^1H NMR (270 MHz, CDCl_3): δ = 8.88 (br s, 1H), 7.46 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 4.45 (s, 1H), 3.72 (d, J = 9.7 Hz, 1H), 3.63 (s, 3H), 3.63-3.52 (m, 1H), 3.44-3.36 (m, 1H), 3.16 (dd, J = 13.0, 4.9 Hz, 1H), 2.93-2.81 (m, 2H), 2.28 (d, J = 14.3 Hz, 1H), 1.93 (br s, 1H); ^{13}C NMR (67.8 MHz, CDCl_3): δ = 170.7, 164.8, 143.8, 131.7, 128.0, 121.2, 82.1, 61.9, 50.7, 50.1, 46.3, 45.9; IR (KBr): 3307, 2947, 2835, 2250, 1655, 1608, 1431, 1299, 1251, 1174 cm^{-1} ; HRMS (FAB): calcd for $\text{C}_{14}\text{H}_{18}\text{BrN}_2\text{O}_2$ [$M + \text{H}$] $^+$: 325.0552, found 325.0556; *Anal.* Calcd for $\text{C}_{14}\text{H}_{17}\text{BrN}_2\text{O}_3$: C, 51.71; H, 5.27; N, 8.61. found C, 51.71; H, 8.68; N, 5.20.

Compound 3e

Pale yellow solid; m.p. 159 °C; ^1H NMR (270 MHz, CDCl_3): δ = 8.89 (br s, 1H), 8.19 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 8.8 Hz, 2H), 4.47 (s, 1H), 3.90 (d, J = 9.5 Hz, 1H), 3.64 (s, 3H), 3.64-3.51 (m, 1H), 3.48-3.40 (m, 1H), 3.21 (dd, J = 13.0, 4.9 Hz, 1H), 2.96-2.85 (m, 2H), 2.29 (d, J = 14.6 Hz, 1H), 2.00 (br s, 1H); ^{13}C NMR (67.8 MHz, CDCl_3): δ = 170.6, 164.1, 151.7, 147.1, 127.2, 123.9, 82.4, 61.9, 50.6, 50.1, 46.2, 45.7; IR (KBr): 3317, 2839 cm^{-1} ; HRMS (FAB): calcd for $\text{C}_{14}\text{H}_{18}\text{N}_3\text{O}_4$ [$M + \text{H}$] $^+$: 292.1297, found 292.1306.

Compound 3f

Colorless solid; m.p. 156-157 °C; ^1H NMR (270 MHz, CDCl_3): δ = 8.88 (br s, 1H), 7.64 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 4.46 (s, 1H), 3.83 (d, J = 9.7 Hz, 1H), 3.63 (s, 3H), 3.63-3.53 (m, 1H), 3.47-3.36 (m, 1H), 3.19 (dd, J = 12.7, 4.3 Hz, 1H), 2.93-2.83 (m, 2H), 2.28 (d, J = 14.6 Hz, 1H), 1.94 (br s, 1H); ^{13}C NMR (67.8 MHz, CDCl_3): δ = 170.6, 164.2, 149.7, 132.4, 127.1, 118.4, 111.4, 82.3, 62.1, 50.5, 50.1, 46.1, 45.7; IR (KBr): 3309, 2947, 2835, 2227, 1654, 1616, 1508, 1306, 1257, 1180 cm^{-1} ; HRMS (FAB): calcd for $\text{C}_{15}\text{H}_{18}\text{N}_3\text{O}_2$ [$M + \text{H}$] $^+$: 272.1399, found 272.1398; *Anal.* Calcd for $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_2$: C, 66.40; H, 6.32; N, 15.49. found C, 66.50; H, 6.30; N, 15.45.

Compound 3g

Colorless solid; m.p. 144-146 °C; ^1H NMR (300 MHz, CDCl_3): δ = 8.90 (br s, 1H), 8.01 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 8.3 Hz, 2H), 4.47 (s, 1H), 3.91 (s, 3H), 3.82 (d, J = 9.6 Hz, 1H), 3.64 (s, 3H), 3.64-3.55 (m, 1H), 3.46-3.37 (m, 1H), 3.19 (dd, J = 12.9, 4.8 Hz, 1H), 2.96-2.84 (m, 2H), 2.31 (d, J = 14.4 Hz, 1H), 1.95 (br s, 1H); ^{13}C NMR (75.5 MHz, CDCl_3): δ = 170.9, 166.7, 165.0, 149.8, 130.1, 129.5, 126.4, 82.2, 62.3, 52.1, 50.6, 50.0, 46.3, 45.8; IR (KBr): 3313, 2951, 2837, 225, 1730, 1662, 1616, 1508, 1437, 1304, 1259, 1180 cm^{-1} ; HRMS (FAB): calcd

for $C_{16}H_{21}N_2O_4$ $[M + H]^+$: 305.1501, found 305.1500; *Anal.* Calcd for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.20. found C, 63.13; H, 6.55; N, 9.12.

Compound 3h

Pale red oil; 1H NMR (300 MHz, $CDCl_3$): δ = 8.94 (br s, 1H), 8.56 (d, J = 4.8 Hz, 1H), 7.67 (ddd, J = 7.5, 7.5, 1.5 Hz, 1H), 7.31 (d, J = 7.5 Hz, 1H), 7.21-7.17 (m, 1H), 4.52 (s, 1H), 3.94 (d, J = 9.9 Hz, 1H), 3.63 (s, 3H), 3.63-3.55 (m, 1H), 3.44-3.35 (m, 1H), 3.22 (dd, J = 13.2, 4.2 Hz, 1H), 3.04-2.85 (m, 2H), 2.49 (d, J = 14.7 Hz, 1H), 2.45 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 170.6, 165.1, 162.0, 149.1, 136.7, 122.2, 120.8, 82.0, 62.1, 49.8, 49.7, 46.8, 44.6; IR (KBr): 3310, 2837, 2251, 1670, 1616, 1508, 1321, 1263, 1196 cm^{-1} ; HRMS (FAB): calcd for $C_{13}H_{18}N_3O_2$: 248.1399, found 248.1407.

Compound 3i

Pale yellow oil; 1H NMR (300 MHz, $CDCl_3$): δ = 8.88 (br s, 1H), 7.22-7.21 (m, 1H), 6.97-6.93 (m, 2H), 4.50 (s, 1H), 4.14 (d, J = 9.3 Hz, 1H), 3.63 (s, 3H), 3.63-3.52 (m, 1H), 3.43-3.34 (m, 1H), 3.16 (dd, J = 13.2, 5.1 Hz, 1H), 2.96-2.82 (m, 2H), 2.50 (d, J = 14.7 Hz, 1H), 2.10 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 170.6, 164.3, 148.1, 126.3, 124.1, 123.0, 82.3, 57.6, 50.2, 50.1, 46.9, 46.3; IR (KBr): 3306, 2947, 2835, 2248, 1651, 1601, 1504, 1433, 1303, 1238, 1174 cm^{-1} ; HRMS (FAB): calcd for $C_{12}H_{17}N_2O_2S$: 253.1011, found 253.1005.

Compound 3j

Pale yellow oil; 1H NMR (300 MHz, $CDCl_3$): δ = 8.94 (br s, 1H), 7.39-7.26 (m, 10H), 5.12 (A in ABq, J = 12.8 Hz, 1H), 5.10 (B in ABq, J = 12.8 Hz, 1H), 4.54 (s, 1H), 3.76 (d, J = 9.9 Hz, 1H), 3.61 (ddd, J = 14.4, 9.9, 4.2 Hz, 1H), 3.45-3.36 (m, 1H), 3.17 (dd, J = 12.9, 4.8 Hz, 1H), 2.99-2.84 (m, 2H), 2.36 (d, J = 14.7 Hz, 1H), 1.66 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 170.1, 165.7, 144.9, 137.3, 128.6, 128.3, 127.7, 127.5, 127.5, 126.2, 82.0, 64.2, 62.3, 50.5, 46.3, 45.9; IR (KBr): 3312, 3032, 2806, 2251, 1601, 1504, 1373, 1302, 1232, 912 cm^{-1} ; HRMS (FAB): calcd for $C_{20}H_{23}N_2O_2$ $[M + H]^+$: 323.1760, found 323.1757.

Compound 3k

Pale yellow oil; 1H NMR (300 MHz, $CDCl_3$): δ = 9.07 (br s, 1H), 7.35-7.23 (m, 5H), 4.51 (s, 1H), 4.00 (d, J = 1.5 Hz, 1H), 3.63 (s, 3H), 3.63-3.55 (m, 1H), 3.38-3.19 (m, 2H), 2.82 (t, J = 13.0 Hz, 1H), 2.50-2.45 (m, 1H), 1.88 (br s, 1H), 1.15 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 171.3, 170.3, 143.9, 128.4, 127.2, 126.7, 81.6, 64.8, 51.2, 50.1, 50.0, 46.0, 10.7; IR (KBr): 3290, 2941, 2810, 2250, 1651, 1607, 1504, 1450, 1303, 1230 cm^{-1} ; HRMS (FAB): calcd for $C_{15}H_{21}N_2O_2$ $[M + H]^+$: 261.1603, found 261.1602.

Compound 3l

Colorless solid; m.p. 42 °C; ^1H NMR (300 MHz, CDCl_3): δ = 9.57 (br s, 1H), 7.40-7.24 (m, 5H), 4.12 (q, J = 7.2 Hz, 2H), 3.73 (d, J = 9.0 Hz, 1H), 3.65-3.56 (m, 1H), 3.40-3.31 (m, 1H), 3.15 (dd, J = 12.6, 4.5 Hz, 1H), 3.01 (dd, J = 14.7, 0.9 Hz, 1H), 2.83 (ddd, J = 12.6, 10.2, 0.9 Hz, 1H), 2.70 (dd, J = 14.7, 9.3 Hz, 1H), 1.98 (s, 1H), 1.78 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.5 MHz, CDCl_3): δ = 171.2, 163.0, 145.6, 128.6, 127.4, 126.1, 86.5, 61.6, 58.8, 50.8, 45.9, 40.2, 14.5, 12.8; IR (KBr): 3271, 2804, 2250, 1728, 1647, 1595, 1458, 1246 cm^{-1} ; HRMS (FAB): calcd for $\text{C}_{16}\text{H}_{23}\text{N}_2\text{O}_2$ [$M + \text{H}$] $^+$: 275.1760 found 275.1746

Compound 3m

Colorless solid; m.p. 151 °C; ^1H NMR (300 MHz, CDCl_3): δ = 8.65 (br s, 1H), 7.46-7.26 (m, 5H), 4.32-4.20 (m, 2H), 3.80 (d, J = 9.6 Hz, 1H), 3.65-3.55 (m, 1H), 3.46-3.37 (m, 1H), 3.18 (dd, J = 12.9, 4.8 Hz, 1H), 2.93-2.73 (m, 4H), 2.59 (d, J = 14.7 Hz, 1H), 1.87 (br s, 1H); ^{13}C NMR (67.8 MHz, CDCl_3): δ = 174.1, 160.4, 145.0, 128.7, 127.6, 126.1, 84.9, 65.0, 61.8, 50.7, 46.5, 42.9, 26.6; IR (KBr): 3315, 3153, 2806, 2251, 1682, 1614, 1454, 1371, 1225, 912, 743 cm^{-1} ; HRMS (FAB): calcd for $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}_2$ [$M + \text{H}$] $^+$: 259.1447, found 259.1453; *Anal.* Calcd for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_2$: C, 69.74; H, 7.02; N, 10.84. found C, 69.73; H, 7.00; N, 10.76.

Compound 3n

White solid; m.p. 95 °C; ^1H NMR (300 MHz, CDCl_3): δ = 8.02 (br s, 1H), 7.32-7.23 (m, 5H), 3.66 (s, 3H), 3.54-3.45 (m, 2H), 3.38-3.22 (m, 2H), 3.14 (dd, J = 14.4, 5.1 Hz, 1H), 2.90 (dd, J = 12.6, 12.6 Hz, 1H), 2.43-2.24 (m, 2H), 2.11 (br s, 1H), 1.48-1.20 (m, 2H); ^{13}C NMR (75.5 MHz, CDCl_3): δ = 168.8, 167.4, 143.2, 128.3, 127.5, 127.4, 93.2, 68.6, 54.1, 51.2, 50.0, 47.4, 27.2, 27.0; IR (KBr): 3321, 2854, 2248, 1654, 1603, 1446, 1263, 1191 cm^{-1} ; HRMS (FAB): calcd for $\text{C}_{16}\text{H}_{21}\text{N}_2\text{O}_2$ [$M + \text{H}$] $^+$: 273.1603, found 273.1616.

Preparation and Physical data of 5a-5d and 6a-6c

Compound 5a

Benzyl bromide (22 μl , 0.19 mmol) was added to a solution of **3a** (30.0 mg, 0.122 mmol) and K_2CO_3 (50 mg, 0.36 mmol) in CH_3CN (1.2 mL) at rt under N_2 . The reaction mixture was stirred at 60 °C for 1 h, cooled to rt, and quenched by water. The mixture was extracted with AcOEt. The organic layer was dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by SiO_2 column chromatography (Hexane/AcOEt = 1/1) to give compound **5a** (40.5 mg, 91%)

as pale yellow solid.

M.p. 130 °C; ^1H NMR (270 MHz, CDCl_3): δ = 8.77 (br s, 1H), 7.45-7.19 (m, 10H), 4.47 (s, 1H), 3.74-3.56 (m, 2H), 3.62 (s, 3H), 3.46 (d, J = 10.0 Hz, 1H), 3.30-3.24 (m, 1H), 3.07-2.90 (m, 3H), 2.35-2.20 (m, 2H); ^{13}C NMR (67.8 MHz, CDCl_3): δ = 170.6, 164.7, 144.6, 139.0, 128.7, 128.2, 128.0, 127.2, 126.7, 126.6, 81.9, 68.3, 59.6, 55.7, 50.0, 44.3, 43.9; IR (KBr): 3311, 2947, 2804, 1651, 1605, 1492, 1433, 1309, 1172 cm^{-1} ; HRMS (FAB): calcd for $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_2$ [$M + \text{H}$] $^+$: 337.1916, found 337.1929.

Compound 5b

n-Butyl iodide (19 μl , 0.17 mmol) was added to a solution of **3a** (29.0 mg, 0.110 mmol) and K_2CO_3 (46 mg, 0.33 mmol) in CH_3CN (1.1 mL) at rt under N_2 . The reaction mixture was stirred under reflux for 1.5 h. Additional *n*-butyl iodide (0.1 mL, 0.88 mmol) was added to the reaction mixture and the resulting solution was stirred under reflux for 4 h, cooled to rt, and quenched by water. The mixture was extracted with AcOEt. The organic layer was dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by SiO_2 column chromatography (Hexane/AcOEt = 2/1) to give compound **5b** (34.6 mg, 100%) as pale yellow solid.

M.p. 71 °C; ^1H NMR (300 MHz, CDCl_3): δ = 8.79 (br s, 1H), 7.35-7.23 (m, 5H), 4.43 (s, 1H), 3.67-3.62 (m, 1H), 3.63 (s, 3H), 3.44-3.34 (m, 2H), 3.17 (dd, J = 13.2, 6.3 Hz, 2H), 2.93 (dd, J = 14.4, 10.2 Hz, 2H), 2.46-2.33 (m, 2H), 2.25 (d, J = 14.4 Hz, 1H), 2.10-2.01 (m, 1H), 1.34-1.26 (m, 2H), 1.16-1.00 (m, 2H), 0.74 (t, J = 7.2 Hz, 3H); ^{13}C NMR (67.8 MHz, CDCl_3): δ = 171.2, 165.4, 144.9, 128.9, 127.5, 127.3, 82.3, 68.1, 56.3, 55.4, 50.4, 44.7, 44.6, 28.5, 20.7, 14.4; IR (KBr): 330.6, 2929, 1660, 1605, 1301, 1234, 1171 cm^{-1} ; HRMS (FAB): calcd for $\text{C}_{18}\text{H}_{27}\text{N}_2\text{O}_2$ [$M + \text{H}$] $^+$: 303.2073, found 303.2068.

Compound 5c

Benzyl chloroformate (16 μl , 0.12 mmol) was added to a solution of **3a** (25.6 mg, 0.104 mmol) and K_2CO_3 (28.4 mg, 0.21 mmol) in $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (1/1) (1 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 25 min, and quenched by saturated aq. NH_4Cl . The mixture was extracted with CH_2Cl_2 . The organic layer was dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by SiO_2 column chromatography (Hexane/AcOEt = 4/1) to give compound **5c** (36.2 mg, 92%) as colorless oil.

^1H NMR (270 MHz, CDCl_3): δ = 8.75 (br s, 1H), 7.33-7.21 (m, 10H), 5.73 (br s, 1H), 5.19 (s, 2H), 4.64 (s, 1H), 4.33-4.18 (m, 1H), 3.63 (s, 3H), 3.58-3.36 (m, 2H), 3.16-2.88 (m, 3H); ^{13}C NMR (67.8 MHz, CDCl_3): δ = 170.5, 162.2, 155.9, 138.1, 136.2, 128.5, 128.4, 128.0, 127.7, 127.3, 126.6, 84.6, 67.7, 55.4, 50.1, 44.2, 42.7, 39.1; IR (KBr): 3299, 2948, 2249, 1660, 1599, 1494, 1125 cm^{-1} ; HRMS (FAB): calcd for $\text{C}_{22}\text{H}_{25}\text{N}_2\text{O}_4$: 381.1814, found 381.1819.

Compound 5d

p-Toluenesulfonyl chloride (416 mg, 2.18 mmol) and 4-dimethylaminopyridine (16 mg, 0.13 mmol) was added to a solution of **3a** (316 mg, 1.28 mmol) and triethylamine (1.4 mL, 10 mmol) in CH₂Cl₂ (6.4 mL) at 0 °C under N₂. The reaction mixture was stirred for 10 h at rt, and quenched by sat. aq. NH₄Cl. The mixture was extracted with AcOEt. The organic layer was dried over Na₂SO₄ and evaporated in vacuo. The residue was purified by SiO₂ column chromatography (Hexane/AcOEt = 2/1) to give compound **5d** (481 mg, 94%) as pale yellow solid.

M.p. 165 °C; ¹H NMR (270 MHz, CDCl₃): δ = 8.61 (br s, 1H), 7.67 (d, *J* = 8.6 Hz, 2H), 7.30-7.22 (m, 7H), 5.54-5.50 (m, 1H), 4.54 (s, 1H), 4.05-3.98 (m, 1H), 3.58 (s, 3H), 3.59-3.18 (m, 3H), 3.16-2.94 (m, 2H), 2.42 (s, 3H); ¹³C NMR (67.8 MHz, CDCl₃): δ = 170.1, 161.7, 143.3, 137.5, 136.7, 129.6, 128.4, 127.3, 126.9, 126.8, 85.3, 56.2, 50.1, 44.7, 44.2, 39.5, 21.5; IR (KBr): 3305, 2925, 2252, 1651, 1606, 1496, 1433, 1244, 1159 cm⁻¹; HRMS (FAB): calcd for C₂₁H₂₅N₂O₄S: 401.1535, found 401.1542.

Compound 6a

Acryloyl chloride (10 μl, 0.12 mmol) was added to a solution of **5d** (25.5 mg, 0.064 mmol) in THF (1.3 mL) at RT under N₂. The reaction mixture was stirred for 1 h, and evaporated in vacuo. The residue was purified by SiO₂ column chromatography (Hexane/AcOEt = 5/3) to give compound **6a** (23.9 mg, 82 %) as colorless oil.

¹H NMR (300 MHz, CDCl₃): δ = 7.63 (d, *J* = 8.4 Hz, 2H), 7.30-7.18 (m, 8H), 5.73-5.68 (m, 1H), 4.16-4.01 (m, 3H), 3.92-3.88 (m, 1H), 3.76 (s, 3H), 3.68-3.62 (m, 1H), 3.35-3.28 (m, 1H), 2.60-2.52 (m, 1H), 2.40 (s, 3H), 2.31-2.22 (m, 2H), 2.08-2.00 (m, 1H); ¹³C NMR (75.5 MHz, CDCl₃): δ = 170.2, 167.5, 148.5, 143.4, 137.7, 137.6, 129.7, 128.5, 127.3, 127.0, 126.4, 109.7, 57.1, 51.7, 43.3, 40.3, 33.4, 30.3, 21.5, 21.0; IR (KBr): 2951, 2253, 1683, 1624, 1380, 1329, 1275, 1161 cm⁻¹; HRMS (FAB): calcd for C₂₄H₂₇N₂O₅S [*M* + *H*]⁺: 455.1641, found 455.1648.

Compound 6b

trans-β-Nitrostyrene (15 mg, 0.1 mmol) was added to a solution of **5d** (26.5 mg, 0.066 mmol) in EtOH (1 mL) at rt under N₂. The reaction mixture was stirred under reflux for 8 h, cooled to rt, and evaporated in vacuo. The residue was purified by SiO₂ column chromatography (Hexane/AcOEt = 3/1) to give compound **6b** (18.6 mg, 56 %) as pale yellow oil.

¹H NMR (300 MHz, CDCl₃): δ = 7.74 (d, *J* = 8.1 Hz, 2H), 7.31-7.17 (m, 12H), 6.26 (s, 1H), 5.61-5.58 (m, 1H), 4.51 (dd, *J* = 16.2, 6.0 Hz, 1H), 4.25-4.06 (m, 2H), 3.92-3.85 (m, 1H), 3.65 (s, 3H), 3.43-3.28 (m, 2H), 2.83 (s, 3H); ¹³C NMR (67.8 MHz, CDCl₃): δ = 166.0, 143.5, 138.0,

137.1, 136.3, 135.2, 129.9, 128.8, 128.5, 127.5, 127.2, 127.0, 126.9, 126.1, 125.8, 121.3, 112.4, 57.5, 50.7, 50.6, 42.9, 29.9, 21.6; IR (KBr): 3060, 2927, 2252, 1693, 1608, 1521, 1330, 1292, 1159 cm^{-1} ; HRMS (FAB): calcd for $\text{C}_{29}\text{H}_{28}\text{N}_2\text{O}_4\text{SNa}$ $[M + \text{Na}]^+$: 523.1667, found 523.1672.

Compound 6c

Formaldehyde solution (40 % in water, 0.1 mL, 1.3 mmol) and *t*-butylamine (33 μL , 0.3 mmol) was added to a solution of **5d** (25.2 mg, 0.063 mmol) in CH_3CN (1 mL) at rt. The reaction mixture was stirred at 70 $^\circ\text{C}$ for 0.5 h, cooled to rt, and evaporated in vacuo. The residue was purified by SiO_2 column chromatography (Hexane/AcOEt/TEA= 1/1/trace) to give compound **6c** (30.8 mg, 98%) as pale yellow amorphous.

^1H NMR (300 MHz, CDCl_3): δ = 7.65 (d, J = 8.1 Hz, 2H), 7.38-7.20 (m, 7H), 5.67 (dd, J = 9.6, 6.6 Hz, 1H), 4.17 (dd, J = 14.4, 6.6 Hz, 1H), 3.95 (dt, J = 14.4, 7.2 Hz, 1H), 3.74 (s, 3H), 3.66-3.56 (m, 2H), 3.47-3.35 (m, 2H), 3.17-3.01 (m, 3H), 2.89 (d, J = 14.4 Hz, 1H), 2.39 (s, 3H), 1.04 (s, 9H); ^{13}C NMR (75.5 MHz, CDCl_3): δ = 167.6, 154.2, 143.0, 139.8, 138.1, 129.5, 128.6, 127.2, 127.1, 126.3, 97.5, 65.3, 56.9, 53.0, 50.7, 48.7, 44.8, 42.5, 34.4, 26.1, 21.5; IR (KBr): 2970, 1676, 1577, 1332, 1283, 1161 cm^{-1} ; HRMS (EI): calcd for $\text{C}_{27}\text{H}_{35}\text{N}_3\text{O}_4\text{S}$ $[M]^+$: 497.2348, found 497.2347.

Mechanistic Experiment

Equimolar (1.5 mmol) of benzaldehyde, ethylenediamine, and methyl acetoacetate were stirred with TFA (0.1 equiv.) in CDCl_3 (15 mL) at rt and the reaction was monitored by ^1H NMR. ^1H NMR was measured after 15 min, 1 h, 3 h, 6 h, and 1 day. (See chart A and B)

From the comparison of ^1H NMR chart of benzaldehyde, disappearance of aldehyde and appearance of imine were observed around 8.3 ppm even after 15 min. (See chart A)

From the comparison of ^1H NMR chart of methyl acetoacetate, characteristic enamino ester's peaks¹ (hydrogen bonding NH proton around 8.65 ppm and vinylic proton on α -carbon around 4.45 ppm) were also observed. Disappearance of singlet peak of $\text{CH}_3\text{C}=\text{O}$ at 2.53 ppm and appearance of another singlet peak around 1.9 ppm (probably methyl proton of enamino ester's γ -carbon) was also observed. (See chart A and B)

From chart B, even after reaction mixture was stirred for 1 day at rt, compound **3a** was not produced. Then it was heated to reflux and stirred for additional 20 h and measured ^1H NMR. (See chart C) From this chart, compound **3a** was confirmed to be produced. (See also ^1H NMR of compound **3a**)

Chart A: Reaction mixture after 15 min, 1 h, 3 h, and 6 h

Chart B: Reaction mixture after 1 day

Chart C: Reaction mixture after reflux for 20 h

Reference

(1) For examples see. Zhang, Z.-H.; Yin, L.; Wang, Y.-M. *Adv. Synth. Catal.* **2006**, *348*, 184-190. and its supporting information.

Cf. ^1H NMR of benzaldehyde

Cf. ¹H NMR of methyl acetoacetate

Chart A: Reaction mixture after 15 min, 1 h, 3 h, and 6 h

Chart B: Reaction mixture after 1 day

Chart C: Reaction mixture after reflux for 20 h

¹H NMR of compound 3a

¹³C NMR of compound 3a

¹H NMR of compound 3b

¹³C NMR of compound 3b

¹H NMR of compound 3c

¹³C NMR of compound 3c

¹H NMR of compound 3d

¹³C NMR of compound 3d

¹H NMR of compound 3e

¹³C NMR of compound 3e

¹H NMR of compound 3f

¹³C NMR of compound 3f

¹H NMR of compound 3g

¹³C NMR of compound 3g

¹H NMR of compound 3h

¹³C NMR of compound 3h

¹H NMR of compound 3i

¹³C NMR of compound 3i

¹H NMR of compound 3j

¹³C NMR of compound 3j

¹H NMR of compound 3k

NOE of compound 3k

¹³C NMR of compound 3k

¹H NMR of compound 3l

¹³C NMR of compound 3l

¹H NMR of compound 3m

¹³C NMR of compound 3m

¹H NMR of compound 3n

H-H COSY (2.5-4.0 ppm) of compound 3n

NOE of compound 3n

¹³C NMR of compound 3n

¹H NMR of compound 5a

¹³C NMR of compound 5a

¹H NMR of compound 5b

¹³C NMR of compound 5b

¹H NMR of compound 5c

¹³C NMR of compound 5c

¹H NMR of compound 5d

¹³C NMR of compound 5d

¹H NMR of compound 6a

¹³C NMR of compound 6a

¹H NMR of compound 6b

COC(=O)c1cc(C2=CC=CC=C2)c3nc(ccc3n2C4=CC=CC=C4)C5=CC=CC=C5

6b

¹³C NMR of compound 6b

¹H NMR of compound 6c

¹³C NMR of compound 6c

1817C

DFILE E:\1817C.als
 COMNT 1817C
 DATIM Thu Nov 09 14:56:19 2006
 OBNUC 13C
 EXMOD BCM
 OBFRQ 75.45 MHz
 OBSET 124.00 KHz
 OBFIN 1840.00 Hz
 POINT 32768
 FREQU 20356.23 Hz
 SCANS 472
 ACQTM 1.6097 sec
 PD 1.3900 sec
 PW1 4.50 usec
 IRNUC 1H
 CTEMP 21.3 C
 SLANT CDCL3
 EXREF 77.00 ppm
 BF 0.12 Hz
 RGAIN 24