Supplementary Materials: Green High-Yielding One-Pot Approach to Biginelli Reaction under Catalyst-Free and Solvent-Free Ball Milling Conditions

Mohamed Ould M’hamed, Abdulrahman G. Alshammari and O. M. Lemine

1. General Information

The ball mill used in this study was a Planetary Micro Mill PULVERISSETTE 7 classic line with 45 mL tempered steel vials and 10 mm tempered steel grinding balls. The melting points were determined with a Stuart SMP10 melting point apparatus. All of the compounds used in this study were purchased from Aldrich. IR spectra were obtained with an FT-IR-Tensor 27 spectrometer in KBr pellets. 1H and 13C-NMR spectra were determined with a Bruker 400 NMR spectrometer in DMSO-d6 with trimethylsiline (TMS) as the internal standard. Chemical shifts were expressed as δ ppm units. The elemental analysis was performed on a PerkinElmer 2400 CHN Elemental Analyzer. The progress of all reactions was monitored through TLC on silica gel 60 (Merck) with 1:1 hexane/ethyl acetate.

2. General Procedure for Synthesis of 1,2,3,4-Tetrahydropyrimidines Compound 4a

An equimolar amount (0.02 mol) of benzaldehyde (1a), ethyl acetoacetate (2), and urea (3a) (total mass 5.92 g) was placed into tempered steel vials with 47.36 g of tempered steel balls (10 mm in diameter). The vials were closed and then placed in a Planetary Micro Mill Pulverisette 8. The tetrahydropyrimidine compound 4a was obtained in pure form after 30 min of milling without further purification.

3. Characteristic Data for 1,2,3,4-Tetrahydropyrimidines 4a–l

**Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a).** IR (KBr, νmax, cm⁻¹): 3252, 3109, 2972, 1728, 1689, 1645, 1468, 1230, 1097, 778. 1H-NMR (400 MHz, DMSO-d6) δ 9.19 (s, 1H), 7.74 (s, 1H), 7.37–7.19 (m, 5H), 5.15 (d, J = 3.3 Hz, 1H), 3.99 (q, J = 7.1 Hz, 2H), 2.28 (s, 1H), 1.10 (t, J = 7.1 Hz, 3H); 13C-NMR (100 MHz, DMSO-d6) δ 165.30, 152.09, 148.32, 144.83, 128.35, 127.22, 126.21, 99.22, 59.14, 53.92, 17.74, 14.04. Anal. Calcd for C15H18N2O3: C, 64.62; H, 6.15; N, 10.72. Found: C, 64.58; H, 6.13; N, 10.72.

**Ethyl 6-methyl-4-(4-methylphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4b).** IR (KBr, νmax, cm⁻¹): 3220, 3100, 1720, 1700; 1H-NMR (400 MHz, DMSO-d6) δ 9.12 (s, 1H), 7.67 (s, 1H), 7.11 (s, 3H), 5.12 (d, J = 2.67 Hz, 1H), 3.98 (d, J = 7.08 Hz, 2H), 2.25 (s, 6H), 1.11 (t, J = 7.08 Hz, 3H); 13C-NMR (100 MHz, DMSO-d6) δ 166.3, 153.2, 148.9, 142.7, 137.3, 129.8, 126.9, 100.4, 60.0, 54.5, 21.4, 18.6, 14.9. Anal. (%): calcd for C16H18N2O3 (274.35): C, 65.67; H, 6.61; N, 10.21. found: C, 65.56; H, 6.74; N, 10.02.

**Ethyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4c).** IR (KBr, νmax, cm⁻¹): 3242, 2979, 1706, 1647, 783; 1H-NMR (400 MHz, DMSO-d6) δ 9.24 (s, 1H), 7.76 (s, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 5.14 (d, J = 3.3 Hz, 1H), 3.98 (q, J = 7.1 Hz, 1H), 2.25 (s, 3H), 1.09 (t, J = 7.1 Hz, 3H); 13C-NMR (100 MHz, DMSO-d6) δ 165.17, 151.89, 148.69, 143.76, 131.74, 128.36, 128.15, 98.78, 59.22, 53.37, 17.76, 14.03.

**Ethyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4d).** IR (KBr, νmax, cm⁻¹): 3230, 3204, 1688, 1664; 1H-NMR (400 MHz, DMSO-d6) δ 9.16 (s, 1H), 7.68 (1H, s), 7.15 (d, 2H, J = 8.2 Hz), 6.88 (d, J = 8.2 Hz, 2H), 5.43 (s, 5H), 5.09 (s, 1H), 3.98 (q, J = 6.8 Hz, 2H), 3.72 (s, 3H), 3.38 (s, 3H), 2.51 (s, 3H), 2.24 (s, 3H), 1.10 (t, 3H, t, J = 6.9); 13C-NMR (100 MHz, DMSO-d6) δ 165.36, 159.83,
Ethyl 4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4e). 1H-NMR (400 MHz, DMSO-d6) δ 9.32 (s, 1H), 9.11 (s, 1H), 7.62 (s, 1H), 7.03 (d, J = 8.3 Hz, 2H), 6.69 (d, J = 8.3 Hz, 2H), 5.05 (d, J = 2.5 Hz, 1H), 3.97 (q, J = 7.0 Hz, 2H), 2.20 (d, J = 28.8 Hz, 3H), 1.09 (t, J = 7.0 Hz, 3H); 13C-NMR (100 MHz, DMSO-d6) δ 165.39, 156.51, 152.17, 147.69, 135.40, 127.37, 114.94, 99.72, 59.07, 53.41, 17.70, 14.05.

Ethyl 6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4f). 1H-NMR (400 MHz, DMSO-d6) δ 9.36 (s, 1H), 8.22 (d, J = 8.6 Hz, 2H), 7.90 (s, 1H), 7.51 (d, J = 8.6 Hz, 2H), 5.28 (d, J = 3.0 Hz, 1H), 3.99 (q, J = 7.0 Hz, 2H), 2.27 (s, 3H), 1.10 (t, J = 7.1 Hz, 3H); 13C-NMR (100 MHz, DMSO-d6) δ 165.02, 151.96, 151.72, 149.35, 146.68, 127.62, 123.79, 98.14, 59.35, 53.64, 17.83, 14.00.

Ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4g). (KBr, vmax cm⁻¹): 3322, 3466, 3176, 3111, 1670, 1575, 1470; 1H-NMR (400 MHz, DMSO-d6) δ 9.19 (s, 1H), 7.74 (s, 1H), 7.35–7.21 (m, 5H), 5.14 (d, J = 2.7 Hz, 1H), 3.98 (q, J = 7.11 Hz, 2H), 2.25 (s, 3H), 1.09 (t, J = 7.11 Hz, 3H); 13C-NMR (100 MHz, DMSO-d6) δ 174.20, 165.10, 145.00, 143.46, 128.53, 127.65, 126.35, 100.68, 59.56, 54.00, 17.12, 13.97.

Ethyl-6-methyl-4-(4-methylphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4h). m.p. 192–194 °C; IR (KBr, vmax cm⁻¹): 3255, 1659, 1562; 1H-NMR (400 MHz, DMSO-d6) δ 10.27 (s, 1H), 9.58 (s, 1H), 7.16–7.07 (m, 4H), 5.12 (s, 1H), 4.00 (q, J = 7.0 Hz, 2H), 2.27 (s, 3H), 2.25 (s, 3H), 1.10 (t, J = 7.0 Hz, 3H); 13C-NMR (100 MHz, DMSO-d6) δ 174.20, 165.10, 144.9, 140.6, 136.9, 129.1, 126.3, 100.9, 59.6, 53.8, 20.7, 17.2, 14.1; Anal. (%): calcld for C15H18O2N2S: C, 62.02; H, 6.25; N, 9.65. Found: C, 62.00; H, 6.47; N, 9.62.

Ethyl 4-(4-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4i). 1H-NMR (400 MHz, DMSO-d6) δ 10.38 (s, 1H), 9.67 (s, 1H), 7.42 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 8.5 Hz, 2H), 5.17 (d, J = 3.7 Hz, 1H), 4.01 (q, J = 7.0 Hz, 2H), 2.29 (s, 3H), 1.09 (t, J = 7.0 Hz, 3H); 13C-NMR (100 MHz, DMSO-d6) δ 174.22, 164.96, 145.34, 142.34, 132.23, 128.55, 128.28, 100.26, 59.62, 53.41, 17.14, 13.96.

Ethyl 4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4j). m.p. 150–152 °C; IR (KBr, vmax cm⁻¹): 3250, 1651, 1598, 1561; 1H-NMR (400 MHz, DMSO-d6) δ 10.29 (s, 1H), 9.59 (s, 1H), 7.14–6.87 (m, 4H), 5.10 (s, 1H), 3.99 (q, J = 7.20 Hz, 2H), 3.71 (s, 3H), 2.27 (s, 3H), 1.09 (t, J = 7.20 Hz, 3H); 13C-NMR (100 MHz, DMSO-d6) δ 174.0, 165.2, 158.8, 1.7, 135.8, 127.7, 113.9, 101.1, 59.6, 55.1, 53.5, 17.2, 14.1; Anal. (%): calcld for C15H16O3N2S: C, 58.78; H, 5.93; N, 9.15. Found: C, 58.83; H, 5.77; N, 9.03.

Ethyl 4-(4-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4k). FT-IR (KBr, νmax cm⁻¹): 3328, 3201, 2975, 1721, 1565, 1505, 1383, 1260, 1182, 1089, 908, 758, 523; 1H-NMR (400 MHz, DMSO-d6) δ 10.25 (s, 1H), 9.55 (s, 1H), 9.43 (s, 1H), 7.01 (d, J = 4.6 Hz, 2H), 6.71 (d, J = 8.6 Hz, 2H), 5.07 (d, J = 3.7 Hz, 1H), 4.00 (q, J = 7.1 Hz, 2H), 2.28 (s, 3H), 1.10 (t, J = 7.1 Hz, 3H); 13C-NMR (100 MHz, DMSO-d6) δ 173.83, 165.17, 156.86, 144.47, 134.07, 127.61, 115.10, 101.07, 59.46, 53.52, 17.08, 13.99.

Ethyl 6-methyl-4-(4-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4l). 1H-NMR (400 MHz, DMSO-d6) δ 1.12 (t, J = 6.8 Hz, 3H), 2.33 (s, 3H), 4.03 (q, J = 6.8 Hz, 2H), 5.33 (d, J = 3.6 Hz, 1H), 7.51 (d, J = 9.2 Hz, 2H), 8.25 (d, J = 8.8 Hz, 2H), 9.76 (s, 1H), 10.49 (s, 1H); 13C-NMR (100 MHz, DMSO-d6) δ 14.4, 17.7, 54.1, 60.2, 100.2, 124.4, 128.3, 146.4, 147.4, 150.8, 165.3, 175.0.
4. Nuclear Magnetic Resonance (NMR) for Compounds 4a and 4g as Example

**Figure S1.** $^1$H-NMR spectrum of compound 4a.

**Figure S2.** $^{13}$C-NMR spectrum of compound 4a.
Figure S3. $^1$H-NMR spectrum of compound 4g.

Figure S4. $^{13}$C-NMR spectrum of compound 4g.