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

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1. General Information

The ball mill used in this study was a Planetary Micro Mill PULVERISETTE 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. ^{1}H and ^{13}C-NMR spectra were determined with a Bruker 400 NMR spectrometer in DMSO-d_6 with trimethylsilane (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, ν_{max}, cm^{-1}): 3252, 3109, 2972, 1728, 1689, 1645, 1468, 1230, 1097, 778. ^{1}H-NMR (400 MHz, DMSO-d_6) 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); ^{13}C-NMR (100 MHz, DMSO-d_6) 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 $C_{14}H_{16}N_2O_3$: 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, ν_{max}, cm^{-1}): 3220, 3100, 1720, 1700; ^{1}H-NMR (400 MHz, DMSO-d_6) 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); ^{13}C-NMR (100 MHz, DMSO-d_6) 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 $C_{15}H_{18}N_2O_3$ (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, ν_{max}, cm^{-1}): 3242, 2979, 1706, 1647, 783; ^{1}H-NMR (400 MHz, DMSO-d_6) 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); ^{13}C-NMR (100 MHz, DMSO-d_6) 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, ν_{max}, cm^{-1}): 3230, 3204, 1688, 1664; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.16 (s, 1H), 7.68 (1H, s), 7.15 (d, 2 H, *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); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 165.36, 159.83,

158.42, 152.25, 147.96, 137.00, 127.38, 113.66, 99.56, 59.13, 55.01, 53.30, 17.70, 14.06. Anal. Calcd for $C_{15}H_{18}O_4N_2$ (290.31): C, 62.05; H, 6.24; N, 9.64. Found: C, 61.85; H, 6.28; N, 9.66.

Ethyl 4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4e**). ^{1}H-NMR (400 MHz, DMSO-d_6) 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); ^{13}C-NMR (100 MHz, DMSO-d_6) 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**). ^{1}H-NMR (400 MHz, DMSO-d_6) 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); ^{13}C-NMR (100 MHz, DMSO-d_6) 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, ν_{max}, cm^{-1}): 3322, 3466, 3176, 3111, 1670, 1575, 1470; ^{1}H-NMR (400 MHz, DMSO-d_6) 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); ^{13}C-NMR (100 MHz, DMSO-d_6) 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, ν_{max}, cm^{-1}): 3255, 1659, 1562; ^{1}H-NMR (400 MHz, DMSO-d_6) 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); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 174.2, 165.2, 144.9, 140.6, 136.9, 129.1, 126.3, 100.9, 59.6, 53.8, 20.7, 17.2, 14.1; Anal. (%): calcd. for $C_{15}H_{18}O_2N_2S$: 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**). ^{1}H-NMR (400 MHz, DMSO-d_6) 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); ^{13}C-NMR (100 MHz, DMSO-d_6) 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, ν_{max}, cm^{-1}): 3250, 1651, 1598, 1561; ^{1}H-NMR (400 MHz, DMSO-d_6) 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); ^{13}C-NMR (100 MHz, DMSO-d_6) 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. (%): calcd for $C_{15}H_{18}O_3N_2S$: 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, ν_{max}, cm^{-1}): 3328, 3201, 2975, 1721, 1565, 1505, 1383, 1260, 1182, 1089, 908, 758, 523; ^{1}H-NMR (400 MHz, DMSO-d_6) 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); ^{13}C-NMR (100 MHz, DMSO-d_6) 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**). ^{1}H-NMR (400 MHz, DMSO-d_6) 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); ^{13}C-NMR (100 MHz, DMSO-d_6) 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

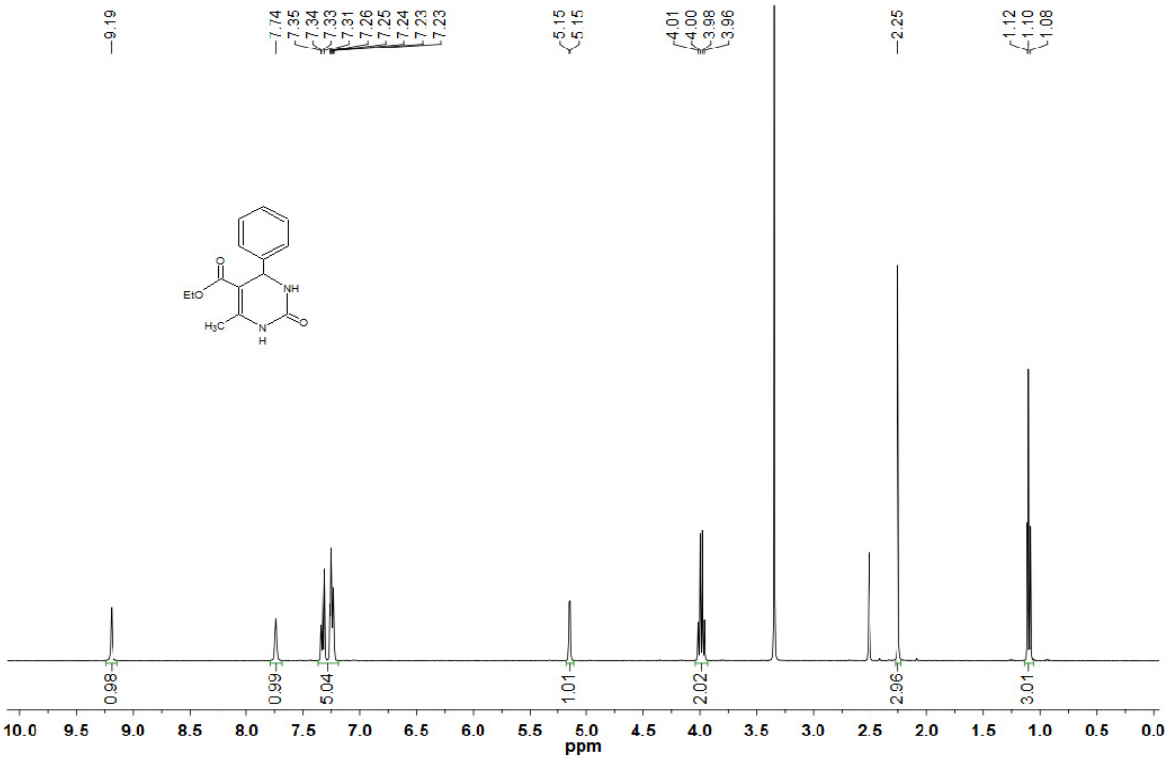

Figure S1. [1]H-NMR spectrum of compound **4a**.

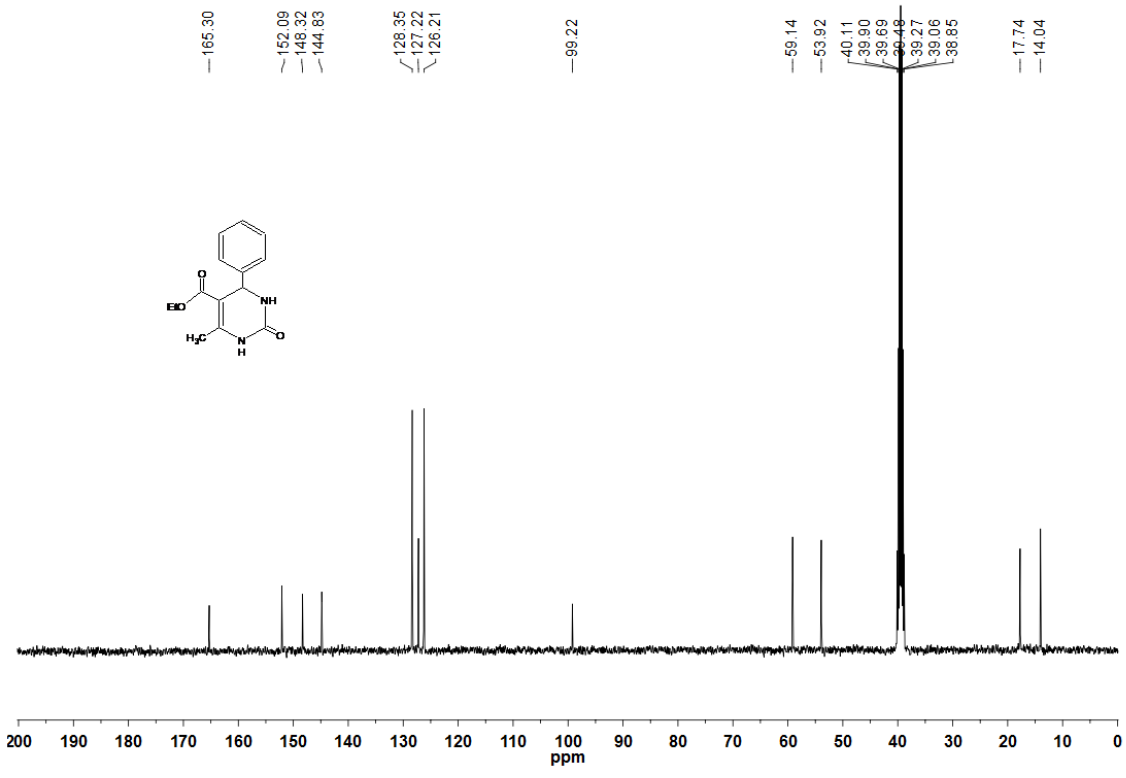

Figure S2. [13]C-NMR spectrum of compound **4a**.

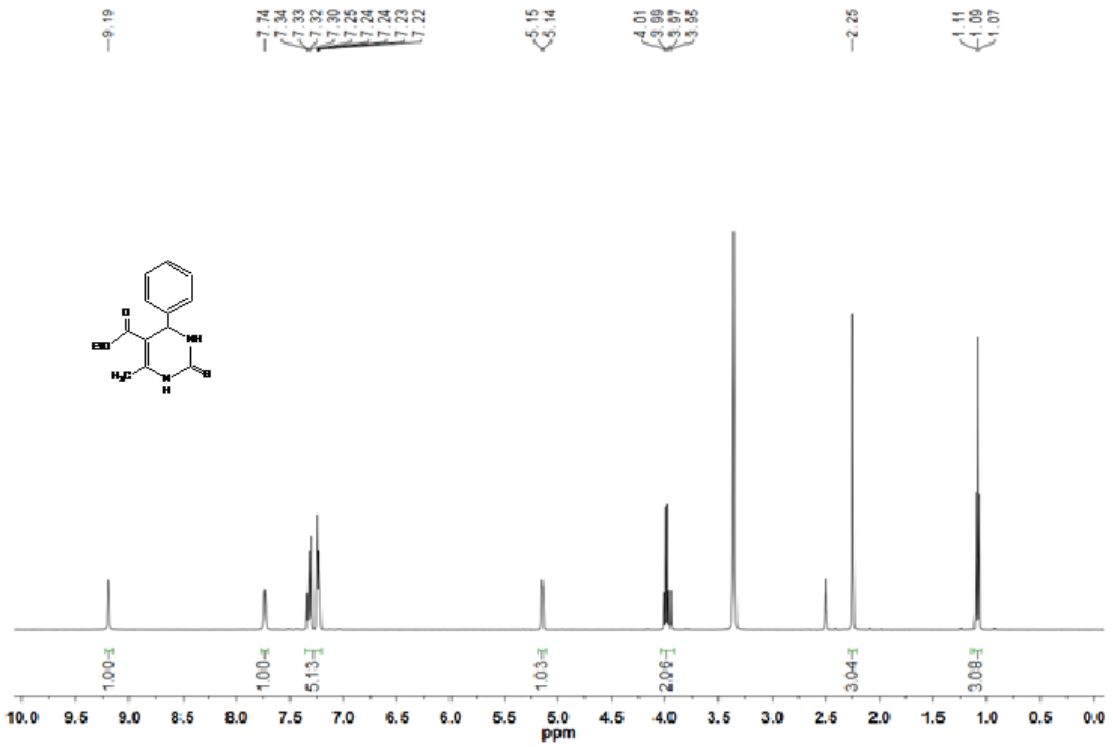

Figure S3. [1]H-NMR spectrum of compound **4g**.

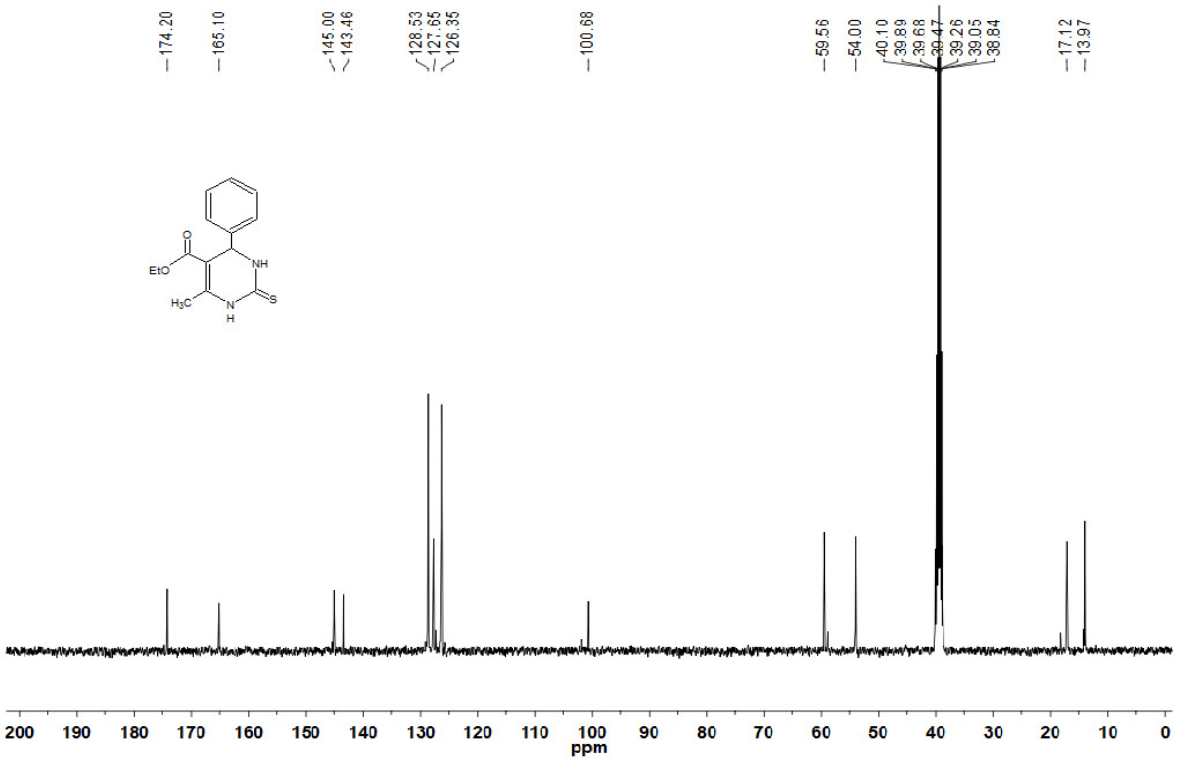

Figure S4. [13]C-NMR spectrum of compound **4g**.