

Supporting Information

for

Sustainable synthesis of 3-substituted phthalides via a catalytic one-pot cascade strategy from 2-formylbenzoic acid with β -keto acids in glycerol

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Experimental procedures, characterization data and copies of NMR spectra

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General information

All reactions were carried out under air. Solvents were purified by standard procedure before use. Commercial solvents were used without further purification. Flash chromatography was performed on silica gel 60 (40–63 μm , 60 Å). Thin layer chromatography (TLC) was performed on glass plates coated with silica gel 60 with F254 indicator. Electrospray ionization high-resolution mass spectra (ESI-HRMS) were recorded on a Bruker P-SIMS-Gly FT-ICR mass spectrometer. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Bruker 600 MHz spectrometer. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent (CHCl_3 , δ 7.26). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker 150 MHz spectrometer. Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent (CDCl_3 , δ 77.07). Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz), integration.

Preparation of β -keto acids^[1]

To a β -keto ester (10 mmol) at room temperature was added aqueous sodium hydroxide (1 N, 20 mL). The mixture was stirred vigorously at room temperature for 12 h, and extracted with CH_2Cl_2 (2 $\times$ 20 mL). The aqueous layer was cooled with ice-water and acidified with aqueous HCl (1 N) until pH $\approx$ 2, and extracted with CH_2Cl_2 (2 $\times$ 60 mL). The combined organic layers were dried over anhydrous sodium sulfate, and evaporated under reduced pressure at a temperature below 30 $^\circ\text{C}$ to give β -keto acid.

Typical procedure for the one-pot cascade reaction

In 25 mL Schlenk flask were placed **1** (0.5 mmol), **2** (1.0 mmol), PMPNH₂ (0.2 mmol, 20 mol %), and 3.0 mL glycerol. The mixture was heated at 65 $^\circ\text{C}$ for 0.5 h, cooled, and extracted three times with ethyl acetate. After concentration under reduced pressure, the resulting residue was purified by column chromatography (SiO_2 ; hexanes/EtOAc 4:1) to give product **3**.

3-(2-Oxo-2-phenylethyl)isobenzofuran-1(3H)-one (3a).^[2] White solid, 80% yield, m.p. = 143–145 $^\circ\text{C}$. ^1H NMR (600 MHz, CDCl_3) δ 7.97 (d, J = 7.9 Hz, 2H), 7.93 (d, J = 7.6 Hz, 1H), 7.67 (t, J = 7.5 Hz, 1H), 7.62 (t, J = 7.4 Hz, 1H), 7.59–7.54 (m, 2H), 7.50 (t, J = 7.7 Hz, 2H), 6.19 (t, J = 6.5 Hz, 1H), 3.79 (dd, J = 17.6, 5.7 Hz, 1H), 3.40 (dd, J = 17.6, 7.4 Hz, 1H). ^{13}C NMR (151 MHz, CDCl_3) δ 196.1, 170.2, 149.8

136.2, 134.3, 133.9, 129.5, 128.9, 128.2, 125.9, 125.8, 122.9, 77.2, 43.7.

3-(2-Oxo-2-(*p*-tolyl)ethyl)isobenzofuran-1(3*H*)-one (3b).^[2] White solid, 81% yield, m.p. = 148-149 °C. ¹H NMR (600 MHz, CDCl₃) δ 7.92 (d, *J* = 7.7 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 2H), 7.66 (td, *J* = 7.7, 1.0 Hz, 1H), 7.58-7.53 (m, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 6.18 (t, *J* = 6.6 Hz, 1H), 3.76 (dd, *J* = 17.5, 5.7 Hz, 1H), 3.36 (dd, *J* = 17.5, 7.5 Hz, 1H), 2.42 (s, 3H). ¹³C NMR (151 MHz, CDCl₃) δ 195.67, 170.2, 149.9, 144.9, 134.3, 133.8, 129.5, 129.4, 128.3, 125.9, 125.8, 122.9, 77.3, 43.6, 21.7.

3-(2-(4-Methoxyphenyl)-2-oxoethyl)isobenzofuran-1(3*H*)-one (3c).^[2] White solid, 82% yield, m.p. = 116-117 °C. ¹H NMR (600 MHz, DMSO) δ 7.99 (d, *J* = 8.9 Hz, 2H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.79 (t, *J* = 7.4 Hz, 1H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.05 (d, *J* = 8.9 Hz, 2H), 6.11 (dd, *J* = 7.8, 4.3 Hz, 1H), 3.85 (s, 3H), 3.75 (dd, *J* = 17.8, 4.3 Hz, 1H), 3.68 (dd, *J* = 17.8, 8.0 Hz, 1H). ¹³C NMR (151 MHz, DMSO) δ 195.2, 170.3, 164.0, 150.5, 134.8, 131.1, 129.7, 129.7, 126.0, 125.4, 123.4, 114.5, 77.8, 56.1, 42.9.

3-(2-(4-Chlorophenyl)-2-oxoethyl)isobenzofuran-1(3*H*)-one (3d).^[2] White solid, 78% yield, m.p. = 145-146 °C. ¹H NMR (600 MHz, CDCl₃) δ 7.93-7.90 (m, 3H), 7.70-7.66 (m, 1H), 7.56 (t, *J* = 6.7 Hz, 2H), 7.47 (d, *J* = 8.6 Hz, 2H), 6.16 (t, *J* = 6.5 Hz, 1H), 3.73 (dd, *J* = 17.6, 6.0 Hz, 1H), 3.37 (dd, *J* = 17.6, 7.1 Hz, 1H). ¹³C NMR (151 MHz, CDCl₃) δ 194.8, 170.0, 149.6, 140.5, 134.5, 134.3, 129.6, 129.6, 129.2, 125.9, 125.8, 122.7, 77.0, 43.7.

3-(2-(4-Fluorophenyl)-2-oxoethyl)isobenzofuran-1(3*H*)-one (3e).^[2] White solid, 75% yield, m.p. = 134-135 °C. ¹H NMR (600 MHz, DMSO) δ 8.10 (dd, *J* = 8.7, 5.6 Hz, 2H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.80 (t, *J* = 7.4 Hz, 1H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.37 (t, *J* = 8.8 Hz, 2H), 6.12 (dd, *J* = 7.9, 4.1 Hz, 1H), 3.85 (dd, *J* = 18.0, 4.1 Hz, 1H), 3.74 (dd, *J* = 18.0, 8.0 Hz, 1H). ¹³C NMR (151 MHz, DMSO) δ 195.6, 170.2, 166.6, 164.9, 150.4, 134.8, 133.5 (d, *J* = 2.5 Hz), 131.7 (d, *J* = 9.6 Hz), 129.8, 126.0, 125.4, 123.4, 116.3 (d, *J* = 21.9 Hz), 77.6, 43.2.

3-(2-(4-Bromophenyl)-2-oxoethyl)isobenzofuran-1(3*H*)-one (3f).^[2] White solid, 79% yield, m.p. = 147-148 °C. ¹H NMR (600 MHz, CDCl₃) δ 7.92 (d, *J* = 7.8 Hz, 1H), 7.82 (d, *J* = 8.5 Hz, 2H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.55 (dd, *J* = 7.3, 4.8 Hz, 2H), 6.16 (t, *J* = 6.5 Hz, 1H), 3.72 (dd, *J* = 17.6, 6.0 Hz, 1H), 3.37 (dd, *J* = 17.6, 7.0 Hz, 1H). ¹³C NMR (151 MHz, CDCl₃) δ 195.0, 170.0, 149.5, 134.9, 134.4, 132.2, 129.7, 129.6, 129.2, 125.9, 125.9, 122.7, 77.0, 43.7.

3-(2-Oxo-2-(*m*-tolyl)ethyl)isobenzofuran-1(3*H*)-one (3g).^[2] White solid, 80% yield, m.p. = 104-105 °C. ¹H NMR (600 MHz, CDCl₃) δ 7.92 (d, *J* = 7.6 Hz, 1H), 7.78 (s, 1H), 7.75 (d, *J* = 7.7 Hz, 1H), 7.67-7.65 (m, 1H), 7.58-7.53 (m, 2H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 6.22-6.13 (m,

1H), 3.77 (dd, $J = 17.6, 5.7$ Hz, 1H), 3.39 (dd, $J = 17.6, 7.4$ Hz, 1H), 2.42 (s, 3H). ^{13}C NMR (151 MHz, CDCl_3) δ 196.3, 170.2, 149.8, 138.7, 136.2, 134.7, 134.3, 129.4, 128.7, 128.7, 125.9, 125.8, 125.4, 122.9, 77.1, 43.8, 21.4.

3-(2-(*m*-Methoxyphenyl)-2-oxoethyl)isobenzofuran-1(3*H*)-one (3h).^[2] White solid, 82% yield, m.p. = 116-117 °C. ^1H NMR (600 MHz, DMSO) δ 7.99 (d, $J = 8.9$ Hz, 2H), 7.86 (d, $J = 7.6$ Hz, 1H), 7.79 (t, $J = 7.4$ Hz, 1H), 7.74 (d, $J = 7.6$ Hz, 1H), 7.61 (t, $J = 7.4$ Hz, 1H), 7.05 (d, $J = 8.9$ Hz, 2H), 6.11 (dd, $J = 7.8, 4.3$ Hz, 1H), 3.85 (s, 3H), 3.75 (dd, $J = 17.8, 4.3$ Hz, 1H), 3.68 (dd, $J = 17.8, 8.0$ Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 195.2, 170.3, 164.0, 150.5, 134.8, 131.1, 129.7, 129.7, 126.0, 125.4, 123.4, 114.5, 77.8, 56.1, 42.9.

3-(2-Oxo-2-(*o*-tolyl)ethyl)isobenzofuran-1(3*H*)-one (3i).^[2] White solid, 65% yield, m.p. = 98-99 °C. ^1H NMR (600 MHz, CDCl_3) δ 7.92 (d, $J = 7.6$ Hz, 1H), 7.68 (t, $J = 7.5$ Hz, 1H), 7.63 (d, $J = 7.6$ Hz, 1H), 7.56 (dd, $J = 15.2, 7.6$ Hz, 2H), 7.41 (t, $J = 7.4$ Hz, 1H), 7.27 (dd, $J = 16.6, 6.7$ Hz, 3H), 6.16 (t, $J = 6.4$ Hz, 1H), 3.67 (dd, $J = 17.4, 6.3$ Hz, 1H), 3.36 (dd, $J = 17.4, 6.7$ Hz, 1H), 2.59 (s, 3H). ^{13}C NMR (151 MHz, CDCl_3) δ 199.3, 170.1, 149.8, 139.0, 136.5, 134.3, 132.4, 132.3, 129.5, 129.0, 126.0, 125.9, 125.8, 122.6, 77.4, 46.2, 21.7.

3-(2-(Naphthalen-2-yl)-2-oxoethyl)isobenzofuran-1(3*H*)-one (3j). White solid, 76% yield, m.p. = 161-162 °C. ^1H NMR (600 MHz, CDCl_3) δ 8.45 (s, 1H), 8.05 (d, $J = 8.6$ Hz, 1H), 7.93 (dd, $J = 13.5, 7.7$ Hz, 3H), 7.89 (d, $J = 8.1$ Hz, 1H), 7.67 (t, $J = 7.5$ Hz, 1H), 7.62 (dd, $J = 12.6, 7.5$ Hz, 2H), 7.56 (dd, $J = 14.6, 7.4$ Hz, 2H), 6.25 (t, $J = 6.5$ Hz, 1H), 3.93 (dd, $J = 17.4, 5.7$ Hz, 1H), 3.54 (dd, $J = 17.4, 7.4$ Hz, 1H). ^{13}C NMR (151 MHz, CDCl_3) δ 196.0, 170.2, 149.8, 135.9, 134.3, 133.6, 132.4, 130.3, 129.7, 129.5, 129.0, 128.8, 127.9, 127.1, 126.0, 125.8, 123.5, 122.9, 77.3, 43.8. HRMS calc. for $[\text{M}+\text{Na}]^+ \text{C}_{20}\text{H}_{14}\text{NaO}_3$: 325.0841, found: 325.0851.

3-(2-Oxo-2-(thiophen-2-yl)ethyl)isobenzofuran-1(3*H*)-one (3k).^[2] White solid, 85% yield, m.p. = 133-134 °C. ^1H NMR (600 MHz, DMSO) δ 8.07 (d, $J = 4.9$ Hz, 1H), 8.02 (d, $J = 3.7$ Hz, 1H), 7.86 (d, $J = 7.6$ Hz, 1H), 7.80 (t, $J = 7.4$ Hz, 1H), 7.75 (d, $J = 7.6$ Hz, 1H), 7.62 (t, $J = 7.4$ Hz, 1H), 7.27-7.25 (m, 1H), 6.10 (dd, $J = 8.3, 3.9$ Hz, 1H), 3.77 (dd, $J = 17.3, 4.0$ Hz, 1H), 3.68 (dd, $J = 17.3, 8.4$ Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 189.8, 170.2, 150.2, 143.8, 136.2, 134.9, 134.8, 129.8, 129.4, 125.9, 125.4, 123.4, 77.6, 43.4.

6,7-Dimethoxy-3-(2-oxo-2-phenylethyl)isobenzofuran-1(3*H*)-one (3l). White solid, 67% yield, m.p. = 129-130 °C. ^1H NMR (600 MHz, CDCl_3) δ 7.95 (dd, $J = 8.4, 1.2$ Hz, 2H), 7.60 (d, $J = 7.4$ Hz, 1H), 7.49 (dd, $J = 11.1, 4.6$ Hz, 2H), 7.17 (dt, $J = 8.3, 4.4$ Hz, 2H), 6.05 (dd, $J = 6.9, 6.1$ Hz, 1H), 4.11 (s, 3H), 3.90

(s, 3H), 3.74 (dd, $J = 17.5, 5.7$ Hz, 1H), 3.35 (dd, $J = 17.5, 7.3$ Hz, 1H). ^{13}C NMR (151 MHz, CDCl_3) δ 196.3, 167.6, 152.8, 148.4, 142.7, 136.3, 133.8, 128.9, 128.2, 119.5, 118.2, 117.3, 75.9, 62.4, 56.9, 44.1. HRMS calc. for $[\text{M}+\text{H}] \text{C}_{18}\text{H}_{17}\text{O}_5$: 313.1076, found: 313.1071.

References

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NMR Spectra















































