Nucleophile- or Photo-induced Synthesis of 3-substituted Phthalides from 2-Formylarylketones

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Supporting Information

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1. General experimental conditions

All ${}^{1}\text{H}$ and ${}^{13}\text{C}$ NMR spectra were recorded at room temp. in CDCl₃ or acetone-d₆ on Bruker instruments (Avance 300, Avance DPX 300, Avance DRX 500). Chemical shifts (δ) are reported in parts per million (ppm) from tetramethylsilane (TMS) using the residual solvent resonance (CDCl₃: 7.26 ppm for ¹H NMR, 77.16 ppm for ¹³C NMR, acetone-d₆: 2.05 ppm for ¹H NMR, 29.8 and 206.3 ppm for ¹³C NMR). Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; brs = broad signal). IR spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer in the ATR mode at room temp. Melting points were determined using a Büchi 510 apparatus and are not corrected. High-resolution mass spectra were recorded on a Finnigan MAT 95 (for ESI). Analytical TLC was carried out using precoated silica gel plates (Merck TLC plates silica gel 60F254). Flash column chromatography was performed using Macherey Nagel silica 60M (0.040- 0.063 mm / 230-240 mesh). Chemicals were purchased from Sigma-Aldrich, Acros, Alfa Aesar or TCI and used without further purification. Solvents were dried as follows: THF was distilled from sodium/benzophenone under argon atmosphere. The photochemical experiments were performed using a Rayonet chamber photoreactor RPR-100, equipped with 16 lamps (400 W, 350 ± 20 nm).

2. General procedures

2.1. General Procedure A: Synthesis of phthalides by nucleophilic catalysis

To a solution of an 2-acyl-benzaldehyde 7 (0.5 mmol) in dry DMSO (7 mL) was added NaCN (2.5 mg, 0.05 mmol, 10 mol%) under an atmosphere of argon and the mixture was heated to 50 °C for 2 to 4 h. The conversion was monitored by TLC. After cooling to room temp. the mixture was quenched with aqueous NH₄Cl and extracted (3x) with EtOAc. The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. Pure products were obtained by column chromatography on silica gel.

2.2. General Procedure B: Synthesis of phthalides under photochemical conditions

A solution of an 2-acyl-benzaldehyde 7 (0.25 mmol) in dry DMSO (3 mL) was set under an atmosphere of argon and the mixture was irradiated in a UV-photoreactor (350 nm) over a period of 3 days. The progress of the reaction was monitored by TLC. The crude product solution was poured into water (40 mL) and extracted with EtOAc (3 x 30 ml). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure.

3. Synthesis of Phthalides from 2-Formylarylketones

3.1. **3-Phenylisobenzofuran-1(3***H***)-one** (*rac*-8a):



Following General Procedure A, the reaction of **7a** (105 mg, 0.5 mmol) afforded *rac*-**8a** (74 mg, 0.35 mmol, 70%) as a colorless solid; mp 113-114 °C; TLC: SiO₂ (cyclohexane/EtOAc = 10:1). ¹H NMR (CDCl₃, 300 MHz): δ = 7.97 (d, *J* = 7.6 Hz, 1H), 7.68-7.63 (m, 1H), 7.58-7.53 (m, 1H), 7.38-7.26 (m, 6H), 6.41 (s, 1H). ¹³C NMR (CDCl₃, 75 MHz): δ = 170.5 (C1), 149.7, 136.5, 134.3, 129.4, 129.3, 129.0, 127.0, 125.7, 125.7, 122.9, 82.7 (C3). IR (ATR) v[cm⁻¹] = 2945, 2910, 1758, 1601, 1593, 1441, 1410, 1395, 1263, 1170, 1064, 935, 750, 736. HRMS (EI) for C₁₄H₁₀O₂: calcd. 210.0681, found 210.0686. Following General Procedure B, the reaction of **7a** (52 mg, 0.25 mmol) in DMSO (3 mL) afforded *rac*-**8a** (42 mg, 0.20 mmol, 81 %).

3.2. 3-(2-Hydroxyphenyl)isobenzofuran-1(3*H*)-one (*rac*-8b):



Following General Procedure A, the reaction of **7b** (113 mg, 0.5 mmol) afforded *rac-***8b** (82 mg, 0.36 mmol, 73%) as a colorless solid; mp 120-122 °C; TLC: SiO₂ (cyclohexane/EtOAc = 4:1). ¹H NMR (CDCl₃, 300 MHz): δ = 7.88 (d, *J* = 7.5 Hz, 1H), 7.53-7.43 (m, 3H), 7.12-7.07 (m, 1H), 6.93-6.87 (m, 2H), 6.73-6.68 (m, 1H), 6.63 (s, 1H), 5.17 (s, 1H). ¹³ C NMR (CDCl₃, 75MHz): δ = 171.0, 155.3, 149.6, 136.5, 132.6, 132.0, 129.9, 127.6, 124.1, 122.9, 122.5, 116.4, 76.7 (C3). IR (ATR) v[cm⁻¹] = 3220, 2935, 2735, 1763, 1598, 1501, 1465, 1450, 1401, 1360, 1315, 1267, 1240, 1202, 751, 735. HRMS (EI) for C₁₄H₁₀O₃: calcd. 226.0630, found 226.0625. Following General Procedure B, the reaction of **7b** (56 mg, 0.25 mmol) in DMSO (3 mL) afforded *rac-***8b** also as a colorless solid (48 mg, 0.21 mmol, 85%).

3.3. 3-*p*-Tolylisobenzofuran-1(3*H*)-one (*rac*-8c):



Following General Procedure A, the reaction of **7c** (112 mg, 0.5 mmol) afforded *rac*-**8c** (71 mg, 0.31 mmol, 63%) as a colorless solid; mp 103-104 °C; TLC: SiO₂ (cyclohexane/EtOAc = 6:1). ¹H NMR (CDCl₃, 300 MHz): δ = 7.96 (d, *J* = 7.4 Hz, 1H), 7.67-7.62 (m, 1H), 7.57-7.52 (m, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.38 (s, 1H), 2.35 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ = 170.5, 140.8, 139.3, 134.5, 133.4, 129.6, 129.4, 127.1, 125.7, 125.5, 122.8, 82.7, 21.2. IR (ATR) v[cm⁻¹] = 2960, 2945, 1749, 1600, 1590, 1440, 1412, 1396, 1260, 1168, 1061, 940, 752, 730. HRMS (EI) for C₁₅H₁₂O₂: calcd. 224.0837, found 224.0842. Following General Procedure B, the reaction of **7c** (56 mg, 0.25 mmol) in DMSO (3 mL) afforded *rac*-**8c** also as a colorless solid (44 mg, 0.19 mmol, 79%).

3.4. 3-(4-Methoxyphenyl)isobenzofuran-1(3*H*)-one (*rac*-8d):



Following General Procedure A, the reaction of **7d** (120 mg, 0.5 mmol) afforded *rac-***8d** (78 mg, 0.32 mmol, 65%) as a colorless solid; mp 110-112 °C; TLC: SiO₂ (cyclohexane/EtOAc = 5:1). ¹H NMR (CDCl₃, 300 MHz): δ = 7.86 (d, *J* = 7.5 Hz, 1H), 7.56-7.53 (m, 1H), 7.49-7.44 (m, 1H), 7.22 (d, *J* = 7.7 Hz, 1H), 7.08 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 6.28 (s, 1H), 3.70 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ = 170.5 (C1), 160.4, 149.7, 134.2, 129.2, 128.7, 128.2, 125.9, 125.5, 122.9, 114.3, 82.7 (C3), 55.3. IR (ATR): v[cm⁻¹] = 2930, 2905, 1760, 1601, 1595, 1460, 1414, 1391, 1261, 1166, 1080, 1061, 945, 755, 734. HRMS (EI) for C₁₅H₁₂O₃: calcd. 240.0786, found 240.0791. Following General Procedure B, the reaction of **7d** (60 mg, 0.25 mmol) in DMSO (3 mL) afforded *rac*-**8d** also as a colorless solid (47 mg, 0.19 mmol, 78%).

3.5. 3-(4-Nitrophenyl)isobenzofuran-1(3*H***)-one (***rac***-8e):**



Following General Procedure A, the reaction of **7e** (127 mg, 0.5 mmol) afforded *rac*-**8e** (79 mg, 0.31 mmol, 62%) as a colorless solid; mp 132-134 °C; TLC: SiO₂ (cyclohexane/EtOAc = 5:1). ¹H NMR (300 MHz, CDCl₃) δ = 8.30-8.26 (m, 2H), 8.10-8.01 (m, 1H), 7.72-7.61 (m, 1H), 7.49-7.44 (m, 2H), 7.23-7.19 (m, 2H), 6.51 (s, 1H). ¹³C NMR (75 MHz, CDCl₃) δ = 170.3 (C1), 149.6, 145.5, 145.4, 133.4, 131.4, 129.1, 128.6, 125.1, 124.4, 123.0, 82.8 (C3). IR (ATR): v[cm⁻¹] = 2960, 2914, 1755, 1600, 1591, 1465, 1413, 1390, 1265, 1164, 1065, 950, 750, 739. HRMS (EI) for C₁₄H₉NO₄: calcd. 255.0532, found 255.0538. Following General Procedure B, the reaction of **7e** (64 mg, 0.25 mmol) in DMSO (3 mL) afforded *rac*-**8e** also as a colorless solid (48 mg, 0.19 mmol, 75%).

3.6. 3-(4-Bromophenyl)isobenzofuran-1(3H)-one (rac-8f):



Following General Procedure A, the reaction of **7f** (144 mg, 0.5 mmol) afforded *rac***8f** (88 mg, 0.30 mmol, 61%) as a colorless solid; mp 141-143 °C; TLC: SiO₂ (cyclohexane/EtOAc = 5:1). ¹H NMR (300 MHz, CDCl₃): δ = 7.99-7.96 (m, 1H), 7.68-7.51 (m, 4H), 7.34-7.30 (m, 1H), 7.18-7.15 (m, 2H), 6.37 (s, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 170.2 (C1), 149.28, 135.6, 134.5, 132.2, 129.6, 128.6, 125.8, 125.8, 125.6, 125.5, 123.5, 122.8, 81.9 (C3). IR (ATR): v[cm⁻¹] = 2950, 2910, 1760, 1605, 1595, 1460, 1410, 1385, 1260, 1189, 1050, 953, 756, 741. HRMS (EI) for C₁₄H₉O₂Br: calcd. 287.9786, found 287.9780. Following General Procedure B, the reaction of **7f** (72 mg, 0.25 mmol) in DMSO (3 mL) afforded *rac***8f** also as a colorless solid (60 mg, 0.21 mmol, 83%).

3.7. 3-(Pyridin-4-yl)isobenzofuran-1(3H)-one (rac-8g):



Following General Procedure A, the reaction of **7g** (105 mg, 0.5 mmol) afforded *rac*-**8g** (76 mg, 0.36 mmol, 72%) as a colorless oil; TLC: SiO₂ (EtOAc). ¹H NMR (300 MHz, CDCl₃): $\delta = 8.10-8.08$ (m, 1H), 7.58-7.51 (m, 4H), 7.34-7.30 (m, 1H), 7.18-7.15 (m, 2H), 6.37 (s, 1H). ¹³C NMR (75 MHz, CDCl₃): $\delta = 170.2$ (C1), 149.2, 143.6, 141.5, 132.2, 128.6, 125.5, 123.5, 122.8, 81.9 (C3). IR (ATR): v[cm⁻¹] = 2920, 2890, 1749, 1600, 1590, 1470, 1415, 1380, 1261, 1189, 1080, 950, 760, 738. HRMS (EI) for C₁₃H₉NO₂: calcd. 211.0633, found 211.0638. Following General Procedure B, the reaction of **7g** (52 mg, 0.25 mmol) in DMSO (3 mL) afforded *rac*-**8g** also as a colorless oil (39 mg, 0.18 mmol, 74%).

3.8. 3-Methylisobenzofuran-1(*3H*)-one (*rac*-8h):



Following General Procedure A, the reaction of **7h** (74 mg, 0.5 mmol) afforded *rac*-**8h** (52 mg, 0.35 mmol, 70%) as a colorless oil; TLC: SiO₂ (cyclohexane/EtOAc = 3:1). ¹H NMR (500 MHz, CDCl₃): δ = 7.89 (d, *J* = 7.8 Hz, 1H), 7.66-7.73 (m, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 5.58 (q, *J* = 6.6 Hz, 1H), 1.65 (d, *J* = 6.6 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): δ = 170.4 (C1), 151.1, 134.0, 129.0, 125.7, 125.6, 121.5, 77.7 (C3), 20.3. IR (ATR): v[cm⁻¹] = 2982, 2932, 1759, 1615, 1597, 1460, 1282, 1060, 967, 755, 739. HRMS (EI) for C₉H₈O₂: calcd. 148.0524, found 148.0519. Following General Procedure B, the reaction of **7h** (37 mg, 0.25 mmol) in DMSO (3 mL) afforded *rac*-**8h** also as a colorless oil (26 mg, 0.17 mmol, 71%).

3.9. 3-Ethylisobenzofuran-1(3*H*)-one (*rac*-8i):



Following General Procedure A, the reaction of **7i** (81 mg, 0.5 mmol) afforded *rac*-**8i** (60 mg, 37 mmol, 74%) as a colorless oil; TLC: SiO₂ (cyclohexane/EtOAc = 3:1). ¹H NMR (300 MHz, CDCl₃): δ = 7.90 (d, *J* = 7.2 Hz, 1H), 7.69 (t, *J* = 7.8 Hz, 1H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 5.47 (dd, *J* = 5.1, 6.6 Hz, 1H), 2.09-2.18 (m, 1H), 1.78-1.88 (m, 1H), 1.01 (t, *J* = 7.6 Hz, 3H), ¹³C NMR (75 MHz, CDCl₃): δ = 170.6 (C1), 149.6, 133.9, 128.9, 126.1, 125.4, 121.7, 82.20 (C3), 27.5, 8.7. IR (ATR): v[cm⁻¹] = 2970, 2940, 2880, 1761, 1460, 1285, 1062, 965, 754, 737. HRMS (EI) for C₁₀H₁₀O₂: calcd. 162.0681, found 162.0676. Following General Procedure B, the reaction of **7i** (37 mg, 0.25 mmol) in DMSO (3 mL) afforded *rac*-**8i** also as a colorless oil (30 mg, 0.19 mmol, 75%).

3.10. Pestalalactone (*rac*-6a):



Following General Procedure A, the reaction of pestalone (**5a**) (30 mg, 0.068 mmol) with NaCN afforded pestalalactone *rac*-**6a** (19 mg, 0.042 mmol, 62% yield) as a colorless solid, mp 195-197 °C; TLC: SiO₂ (cyclohexane/EtOAc = 1:2). ¹H NMR: (500 MHz, acetone-d₆): $\delta = 1.37$ (s, 3H), 1.38 / 1.45 (s, 3H), 2.46 / 2.47 (s, 3H), 2.60-3.15 (m, 2H), 3.32 / 3.99 (s, 3H), 4.51 / 4.55 (t, *J* = 5.5 Hz, 1H), 6.44 / 6.49 (s, 1H), 6.80 / 6.96 (s, 1H); ¹³C NMR (125 MHz, Acetone-d₆): $\delta = 171.8$ / 171.9 (s, C1), 163.1 / 163.4, 156.5 / 156.7, 155.3 / 156.4, 151.5 / 152.5, 150.9 / 151.18, 137.2 / 137.4, 131.6 / 131.7, 122.6 / 122.7, 120.5 / 120.9, 118.4 / 118.8, 118.0 / 117.4, 115.5 / 115.7, 104.8 / 105.3, 102.7 / 103.0, 75.3 / 76.0, 61.1 / 62.8, 25.5 / 25.5, 24.6 / 24.7, 18.4, 17.6 / 17.7. IR (ATR): v[cm⁻¹] = 3370, 3221, 2925, 120.5

2850, 1712, 1625, 1521, 1440, 1390, 1365, 1281, 1170, 1150, 1085, 1045, 951, 810, 715. The NMR data are in agreement with those previously reported.

X-ray data for pestalalacton (*rac*-6a)



Identification code	<i>rac-6a CCDC 781113</i>	
Empirical formula C ₂₁ H ₂₀ Cl ₂ O ₆		
Formula weight	439.27	
Crystal system, space group	Monoclinic, P21/c	
Unit cell dimensions	<i>,</i> 1	
а	a 16.959(2) Å	
b	15.4023(10) Å	
С	c 7.7216(10) Å	
β	91.989(4) deg.	
Volume	Volume 2015.7(4) Å ³	
Z, Calculated density	Z, Calculated density 4, 1.447 g/cm ³	
Absorption coefficient	Absorption coefficient 0.358 mm ⁻¹	
F(000) 912		
Crystal size	.1 x .07 x .03 mm	
Theta range for data collection	neta range for data collection 1.79 to 25.00 deg.	
Limiting indices	-20<=h<=19,	
	-14<=k<=18,	
	-7<= <=9	
Reflections collected /	8969 / 3533	
unique	[R(int) = 0.0733]	
Reflection observed [I>2 σ (I)]	1652	
Completeness to theta = 27.00	99.6 %	
Data / restraints / parameters 3533 / 3 / 278		
Goodness-of-fit on F ²	1.053	
Final R indices $[1>2\sigma(1)]$	R1 = 0.0908,	
	wR2 = 0.2423	
R indices (all data)	R1 = 0.1877,	
	WR2 = 0.2882	
Largest diff. peak and hole 1.181 and -0.966 e.		

4. NMR Spectra









Figure 8. ¹³C spectrum of *rac*-8d (75 MHz, CDCl₃).











