

# Efficient Synthesis of 1-Benzyloxyphenyl-3-phenylacetones

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**Abstract:** 1-[(Benzyloxy)phenyl]-3-phenylacetones **1a–c** have been conveniently synthesized by acylation of the PhCH<sub>2</sub>Li-DABCO complex with their respective *N*-methyl *O*-methyl hydroxamates **5a–c**. In four steps, ketones **1a–c** having *ortho*-, *meta*- and *para*-benzyloxy substituents were obtained in 42–51% overall yields from commercially available 2-(hydroxyphenyl)acetic acids.

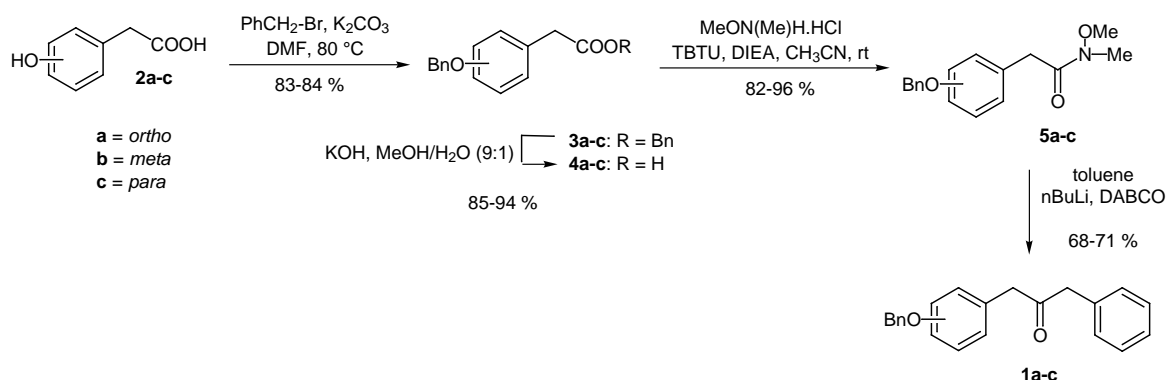
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Protected 1-[(hydroxy)phenyl]-3-phenylacetones are attractive targets because of the importance of 1,3-dibenzylketone as a starting material for the synthesis of polyphenylenes<sup>1,2</sup> and pipercolates.<sup>3</sup> Previous syntheses of *O*-protected 1-[(hydroxy)phenyl]-3-phenylacetones have, however, suffered from low yields and the use of toxic organocadmium reagents.<sup>4–7</sup> Contrary to the low yields obtained in acylations of organocadmium and Grignard reagents,<sup>5–8</sup> acylation of methyllithium with methyl 2-[(3-benzyloxy)phenyl]-*N*-methyl-*O*-methyl hydroxamate (**5b**) gave (3-benzyloxy)phenylacetone in 85% yield.<sup>9</sup> Inspired by this result, we examined the acylation of benzyllithium with *N*-methyl *O*-methyl hydroxamates **5a–c**. By using benzyllithium-DABCO complex in this reaction, we have developed an effective means for synthesizing 1-[(benzyloxy)phenyl]-3-phenylacetones **1a–c** (Scheme).

Commercially available (hydroxyphenyl)acetic acids **2** were alkylated with benzylbromide and K<sub>2</sub>CO<sub>3</sub> in DMF to afford, in 83–84% yields, benzyl benzyloxyphenylacetates **3** that were saponified in MeOH/water (9:1) to their corresponding acids **4** in 85–94% yields. Transformation

of acid **4b** into *N*-methyl-*O*-methyl hydroxamate **5b** was first examined using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSC) and *N*-methyl *O*-methyl hydroxylamine hydrochloride in a THF/water (1:1) solution. 2-[3-(Benzyloxy)phenyl]-*N*-methyl-*O*-methyl hydroxamate (**5b**) was obtained in 80% yield; however, chromatography was needed to isolate pure material. Switching coupling agents from the carbodiimide to the oxonium salt 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU)<sup>10</sup> allowed for the preparation of amide **5b** in higher yield without chromatography. Treatment of acids **4a–c** with TBTU, DIEA and MeON(Me)H•HCl in acetonitrile gave hydroxamates **5a–c** in 82–96% yield. For the final step, benzyllithium was initially generated in the presence of 1,4-diazabicyclo[2,2,2]octane (DABCO) to form the corresponding BnLi-DABCO complex.<sup>11</sup> In the pot, *n*-BuLi was added to a toluene solution containing the diamine and the mixture was heated to 80 °C, when bright yellow crystals formed. The solution was then cooled to room temperature and treated with hydroxamate **5**, the crystals disappeared, and the presence of ketone was detected as a higher R<sub>f</sub> product by TLC. After an aqueous quench and chromatography, ketones **1a–c** were isolated in 68–71% yields.

In summary, this four step route featuring acylation of BnLi-DABCO complex with *N*-methyl-*O*-methyl hydroxamates **5** has furnished 1,3-diphenylacetones **1** with *o*-, *m*- and *p*-benzyloxy substituents in 47%, 51% and 42% respective overall yields.



Scheme

Unless stated otherwise, solvents and reagents were used as supplied. Toluene was distilled from Na and diisopropylethylamine (DIEA) from  $\text{CaH}_2$ . Final reaction solutions were dried over  $\text{Na}_2\text{SO}_4$ . Flash-column chromatography was performed on 230–400 mesh silica gel; TLC was performed on aluminium-backed silica plates with visualization by UV-light, iodine vapour or a ceric ammonium molybdate spray. Mass spectral data, HRMS (FAB) were obtained by the Université de Montréal Mass Spec. Facility.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded in  $\text{CDCl}_3$  at 300 MHz and 100 MHz, respectively. Chemical shifts are in ppm relative to internal TMS for  $^1\text{H}$  NMR spectra and relative to solvent signals for  $^{13}\text{C}$  NMR spectra. Mps were determined on a Gallenkamp melting point apparatus with a digital thermometer.

### Benzyl 2-[(benzyloxy)phenyl]acetates (3); General Procedure

A solution of acid **2** (5.00 g, 32.9 mmol) and  $\text{K}_2\text{CO}_3$  (18.00 g, 131.0 mmol) in DMF (25 mL) was stirred for 15 min. at r.t., treated with benzylbromide (20 mL, 164.5 mmol), stirred for 72 h at 80 °C, cooled to r.t. and quenched with  $\text{H}_2\text{O}$  (20 mL). The pH was adjusted to 4 with citric acid (0.5 N), and the mixture was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 40$  mL). The organic phases were combined, washed with sat.  $\text{NaHCO}_3$  (40 mL) and brine (40 mL), dried and evaporated.

#### Benzyl 2-[2-(benzyloxy)phenyl]acetate (3a)

Purified by crystallization from  $\text{Et}_2\text{O}$ /hexanes.

Yield: 83% (8.80 g); mp: 74.4–74.6 °C;  $R_f$  0.72 (hexanes/ $\text{EtOAc}$ , 4:1).

$^1\text{H}$  NMR:  $\delta$  = 3.76 (s, 2H), 5.07 (s, 2H), 5.11 (s, 2H), 6.93–6.97 (m, 2H), 7.23–7.40 (m, 12H).

$^{13}\text{C}$  NMR:  $\delta$  = 36.4, 66.5, 70.0, 111.9, 120.9, 123.5, 127.2, 127.9, 128.2, 128.5, 128.6, 128.7, 131.2, 136.2, 137.2, 156.8, 171.8.

HRMS: calcd for  $\text{C}_{22}\text{H}_{21}\text{O}_3$  ( $\text{MH}^+$ ) 333.1491. Found: 333.1502.

Anal. calcd for  $\text{C}_{22}\text{H}_{20}\text{O}_3$ ; C, 79.50; H, 6.06. Found: C, 79.08; H, 6.21.

#### Benzyl 2-[3-(benzyloxy)phenyl]acetate (3b)

Purified by chromatography using a gradient of pure hexanes to hexanes/ $\text{EtOAc}$  (95:5).

Yield: 83% (8.80 g);  $R_f$  0.46 (hexanes/ $\text{EtOAc}$ , 4:1).

$^1\text{H}$  NMR:  $\delta$  = 3.66 (s, 2H), 5.04 (s, 2H), 5.15 (s, 2H), 6.90–6.95 (m, 3H), 7.23–7.46 (m, 11H).

$^{13}\text{C}$  NMR:  $\delta$  = 41.5, 66.7, 70.0, 113.8, 115.9, 122.1, 127.6, 128.1, 128.3, 128.4, 128.7, 129.7, 135.5, 136.0, 137.1, 159.1, 171.3.

HRMS: calcd for  $\text{C}_{22}\text{H}_{20}\text{O}_3$  ( $\text{M}^+$ ) 332.1412. Found: 332.1424.

#### Benzyl 2-[4-(benzyloxy)phenyl]acetate (3c)

Purified by crystallization from  $\text{Et}_2\text{O}$ /hexanes.

Yield: 84% (8.90 g); mp: 71.5–71.9 °C (Lit.<sup>12</sup> 69–70 °C);  $R_f$  0.65 (hexanes/ $\text{EtOAc}$ , 4:1).

$^1\text{H}$  NMR:  $\delta$  = 3.48 (s, 2H), 4.91 (s, 2H), 5.00 (s, 2H), 6.81 (d, 2H,  $J$  = 8.7 Hz), 7.08 (d, 2H,  $J$  = 8.7 Hz), 7.19–7.31 (m, 10H).

$^{13}\text{C}$  NMR:  $\delta$  = 40.5, 66.7, 70.1, 115.1, 126.4, 127.6, 128.1, 128.2, 128.3, 128.6, 128.7, 130.5, 136.0, 137.1, 158.1, 171.8.

HRMS: calcd for  $\text{C}_{22}\text{H}_{20}\text{O}_3$  ( $\text{M}^+$ ) 332.1412. Found: 332.1403.

### 2-[(benzyloxy)phenyl]acetic Acids (4); General Procedure

A solution of ester **3** (5.00 g, 15.1 mmol) in  $\text{MeOH}/\text{H}_2\text{O}$  (9:1, 50 mL) was treated with KOH (1.43 g, 25.6 mmol) and THF (5 mL) to improve solubility. The reaction mixture was stirred at r.t. until TLC-analysis indicated the complete consumption of starting material (6–8 h).  $\text{H}_2\text{O}$  (40 mL) was added and the mixture was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 30$  mL). The  $\text{Et}_2\text{O}$  layers were combined, extracted

with sat.  $\text{NaHCO}_3$  (30 mL) and discarded. The alkaline layer was acidified to pH 2 with 1 N HCl and extracted with  $\text{Et}_2\text{O}$  ( $3 \times 30$  mL). Similarly the first  $\text{H}_2\text{O}$  phase was acidified to pH 2 with 1 N HCl and extracted with  $\text{Et}_2\text{O}$  ( $3 \times 20$  mL). The organic layers were combined, dried and evaporated to a solid that was crystallized from  $\text{Et}_2\text{O}$ /hexanes.

#### 2-[2-(benzyloxy)phenyl]acetic Acid (4a)

Yield: 88% (3.22 g); mp: 94.0–94.6 °C (Lit.<sup>13</sup> 94 °C);  $R_f$  0.80 ( $\text{EtOAc}$ ).

$^1\text{H}$  NMR:  $\delta$  = 3.74 (s, 2H), 5.09 (s, 2H), 6.94–7.00 (m, 2H), 7.23–7.42 (m, 7H).

$^{13}\text{C}$  NMR:  $\delta$  = 36.2, 70.1, 112.0, 121.0, 122.9, 127.2, 127.9, 128.7, 129.0, 131.3, 137.1, 156.7, 178.7.

HRMS: calcd for  $\text{C}_{15}\text{H}_{14}\text{O}_3$  ( $\text{M}^+$ ) 242.0943. Found: 242.0953.

#### 2-[3-(benzyloxy)phenyl]acetic Acid (4b)

Yield: 94% (3.44 g); mp: 123.5–124.0 °C (Lit.<sup>14</sup> 123–125 °C);  $R_f$  0.71 ( $\text{MeCN}/\text{MeOH}/\text{H}_2\text{O}$ , 4:1:1).

HRMS: calcd for  $\text{C}_{15}\text{H}_{15}\text{O}_3$  ( $\text{MH}^+$ ) 243.1021. Found: 243.1016.

#### 2-[4-(benzyloxy)phenyl]acetic Acid (4c)

Yield: 85% (3.11 g); mp 119.0–119.5 °C (Lit.<sup>15</sup> 120–121 °C);  $R_f$  0.71 ( $\text{EtOAc}$ ).

$^1\text{H}$  NMR:  $\delta$  = 3.60 (s, 2H), 5.06 (s, 2H), 6.95 (d, 2H,  $J$  = 8.4 Hz), 7.20 (d, 2H,  $J$  = 8.4 Hz), 7.26–7.44 (m, 5H).

$^{13}\text{C}$  NMR:  $\delta$  = 40.4, 70.2, 115.2, 125.8, 127.6, 128.1, 128.8, 130.6, 137.1, 158.3, 178.7.

HRMS: calcd for  $\text{C}_{15}\text{H}_{14}\text{O}_3$  ( $\text{M}^+$ ) 242.0943. Found: 242.0935.

### 2-(benzyloxy)phenyl-*N*-methoxy-*N*-methylacetamides (5); General Procedure

A stirred solution of acid **4** (3.00 g, 12.4 mmol) in  $\text{CH}_3\text{CN}$  (100 mL) was treated with TBTU (4.78 g, 14.9 mmol), DIEA (8.6 mL, 49.6 mmol) and *N,O*-dimethylhydroxylamine·HCl (1.45 g, 14.9 mmol), then stirred at r.t. overnight. The volatiles were removed on a rotary evaporator and the residue was dissolved in  $\text{EtOAc}$  (50 mL), washed with 0.1 N HCl ( $2 \times 20$  mL), 4% aq  $\text{NaHCO}_3$  ( $2 \times 20$  mL) and brine (20 mL), dried and concentrated to provide *N*-methyl *O*-methylhydroxamate **5** suitable for use in subsequent reactions.

#### 2-[2-(benzyloxy)phenyl]-*N*-methoxy-*N*-methylacetamide (5a)

Isolated as a liquid that solidified on standing. The solid was crystallized from  $\text{EtOAc}$ /hexanes.

Yield: 94% (3.31 g); mp: 69.5–71.0 °C;  $R_f$  0.32 ( $\text{CH}_2\text{Cl}_2$ /hexanes, 9:1).

$^1\text{H}$  NMR:  $\delta$  = 3.18 (s, 3H), 3.50 (s, 3H), 3.81 (s, 2H), 5.08 (s, 2H), 6.93–6.96 (m, 2H), 7.24–7.43 (m, 7H).

$^{13}\text{C}$  NMR:  $\delta$  = 32.3, 33.8, 61.0, 70.2, 111.7, 120.9, 124.4, 127.7, 127.9, 128.2, 128.5, 131.2, 137.2, 156.6, 172.7.

HRMS: calcd for  $\text{C}_{17}\text{H}_{20}\text{NO}_3$  ( $\text{MH}^+$ ) 286.1443. Found: 286.1440.

Anal. calcd for  $\text{C}_{17}\text{H}_{19}\text{NO}_3$ ; C, 71.56; H, 6.71; N, 4.91. Found: C, 71.40; H, 6.99; N, 4.95.

#### 2-[3-(benzyloxy)phenyl]-*N*-methoxy-*N*-methylacetamide (5b)

Isolated as a liquid.<sup>9</sup>

Yield: 96% (3.38 g);  $R_f$  0.60 ( $\text{CH}_2\text{Cl}_2$ / $\text{EtOAc}$ /hexanes, 9:1:1).

$^{13}\text{C}$  NMR:  $\delta$  = 32.2, 39.4, 61.3, 69.9, 113.3, 115.8, 122.0, 127.5, 127.9, 128.6, 129.5, 136.5, 137.1, 158.9, 172.2.

HRMS: calcd for  $\text{C}_{17}\text{H}_{20}\text{NO}_3$  ( $\text{MH}^+$ ) 286.1443. Found: 286.1437.

**2-[4-(Benzyloxy)phenyl]-N-methoxy-N-methylacetamide (5c)**

Crystallized from EtOAc/hexanes.

Yield: 82% (2.89 g); mp: 67.5–68.0 °C;  $R_f$  0.39 ( $\text{CH}_2\text{Cl}_2$ /hexanes, 9:1). $^1\text{H}$  NMR:  $\delta$  = 3.20 (s, 3H), 3.63 (s, 3H), 3.73 (s, 2H), 5.06 (s, 2H), 6.95 (d, 2H,  $J$  = 8.5 Hz), 7.25 (d, 2H,  $J$  = 8.5 Hz), 7.35–7.46 (m, 5H). $^{13}\text{C}$  NMR:  $\delta$  = 32.3, 38.5, 61.3, 70.0, 114.9, 127.3, 127.5, 128.0, 128.6, 130.4, 137.1, 157.8, 172.7.HRMS: calcd for  $\text{C}_{17}\text{H}_{20}\text{NO}_3$  ( $\text{MH}^+$ ) 286.1443. Found: 286.1440.Anal. calcd for  $\text{C}_{17}\text{H}_{19}\text{NO}_3$ : C, 71.56; H, 6.71; N, 4.91. Found: C, 71.06; H, 7.01; N, 4.96.**1-[4-(Benzyloxy)phenyl]-3-phenylacetones (1); General Procedure**

A solution of *n*-BuLi (2.5 M in hexanes, 3.5 mL, 8.8 mmol) was added rapidly to a stirred solution of DABCO (0.98 g, 8.8 mmol) in anhyd toluene (25 mL). The color of the mixture became yellow and after heating at 80 °C for 30 min., bright yellow needles were formed indicative of the benzyllithium-DABCO complex. Hereafter, the mixture was cooled to r.t. and treated with a solution of hydroxamate **5** (2.09 g, 7.3 mmol) in dry toluene (21 mL). The yellow needles soon disappeared and the reaction mixture was then stirred for another 60 min., washed with citric acid (0.1 N, 30 mL),  $\text{H}_2\text{O}$  (30 mL), sat.  $\text{NaHCO}_3$  (30 mL) and brine (30 mL), dried and concentrated. Ketone **1** was purified by flash-column chromatography using a gradient of pure hexanes to hexanes/EtOAc (95:5).

**1-[2-(Benzyloxy)phenyl]-3-phenylacetone (1a)**

Solid.

Yield: 69% (1.61 g); mp: 45.8–46.4 °C;  $R_f$  0.64 (hexanes/EtOAc, 4:1). $^1\text{H}$  NMR:  $\delta$  = 3.70 (s, 2H), 3.76 (s, 2H), 5.06 (s, 2H), 6.94–6.99 (m, 2H), 7.08–7.16 (m, 3H), 7.25–7.43 (m, 9H). $^{13}\text{C}$  NMR:  $\delta$  = 44.1, 49.2, 70.0, 111.7, 120.9, 123.7, 126.8, 127.5, 128.0, 128.5 (2), 128.6, 129.5, 131.4, 134.3, 136.9, 156.5, 205.9.HRMS: calcd for  $\text{C}_{22}\text{H}_{21}\text{O}_2$  ( $\text{MH}^+$ ) 317.1541. Found: 317.1547.Anal. calcd for  $\text{C}_{22}\text{H}_{20}\text{O}_2$ : C, 83.52; H, 6.37. Found: C, 82.88; H, 6.91.**1-[3-(Benzyloxy)phenyl]-3-phenylacetone (1b)**Crystallized from Et<sub>2</sub>O/c-hexane.Yield: 68% (1.59 g); mp: 39.5–40.0 °C;  $R_f$  0.48 (hexanes/EtOAc, 4:1). $^1\text{H}$  NMR:  $\delta$  = 3.74 (s, 2H), 3.76 (s, 2H), 5.08 (s, 2H), 6.84 (m, 2H), 6.96 (m, 1H), 7.20–7.51 (m, 11H). $^{13}\text{C}$  NMR:  $\delta$  = 49.1, 49.2, 70.0, 113.6, 116.1, 122.2, 127.1, 127.6, 128.1, 128.7, 128.8, 129.6, 129.9, 134.1, 135.6, 137.0, 159.1, 205.6.HRMS: calcd for  $\text{C}_{22}\text{H}_{21}\text{O}_2$  ( $\text{MH}^+$ ) 317.1541. Found: 317.1547.Anal. calcd for  $\text{C}_{22}\text{H}_{20}\text{O}_2$ : C, 83.52; H, 6.37. Found: C, 83.70; H, 6.59.**1-[4-(Benzyloxy)phenyl]-3-phenylacetone (1c)**Crystallized from Et<sub>2</sub>O/petroleum ether.Yield: 71% (1.66 g); mp: 49.4–49.8 °C;  $R_f$  0.43 (hexanes/EtOAc, 4:1). $^1\text{H}$  NMR:  $\delta$  = 3.68 (s, 2H), 3.73 (s, 2H), 5.07 (s, 2H), 6.94–6.96 (m, 2H), 7.07–7.10 (m, 2H), 7.15–7.19 (m, 2H), 7.27–7.47 (m, 8H). $^{13}\text{C}$  NMR:  $\delta$  = 48.3, 49.1, 70.1, 115.2, 126.5, 127.1, 127.6, 128.1, 128.7, 128.8, 129.6, 130.7, 134.2, 137.1, 158.0, 206.1.HRMS: calcd for  $\text{C}_{22}\text{H}_{20}\text{O}_2$  ( $\text{M}^+$ ) 316.1463. Found: 316.1470.Anal. calcd for  $\text{C}_{22}\text{H}_{20}\text{O}_2$ : C, 83.52; H, 6.37. Found: C, 83.51; H, 6.60.**Acknowledgement**

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