Ionic Hydrogenation of Phthalides: An Efficient Route to *o*-Benzylbenzoic Acids

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The formation of *o*-benzylbenzoic acids **2** from 3-aryl phthalides **1** using triethylsilane/titanium tetrachloride as reducing agent is described.

In connection with the synthesis of some natural products, we needed substituted *o*-benzylbenzoic acids **2**. A possible route for these is the catalytic hydrogenolysis of 3-arylphthalides **1**, which are readily available, for example, by aromatic lithiation reactions[1] or by halogen metal exchange reactions.[2,3] However, we encountered difficulties in the hydrogenolysis reaction. Thus, hydrogenolysis using palladium on carbon as catalyst, although successful in some cases (e.g. **1a, 1d**), did not proceed in others (e.g. **1f, 1g**). Even where catalytic hydrogenolysis succeeded, the yields were not reproducible in our hands, presumably because of the quality of the catalyst.

Ionic hydrogenation of an alcohol group by triethylsilane/trifluoroacetic acid is known[4] to proceed in good yield. In the reaction, an intermediate carbenium ion is generated by the strong acid and trapped by the silane. It was presumed that ionic hydrogenation would also proceed with lactones which are able to yield carbenium ions on treatment with acid.

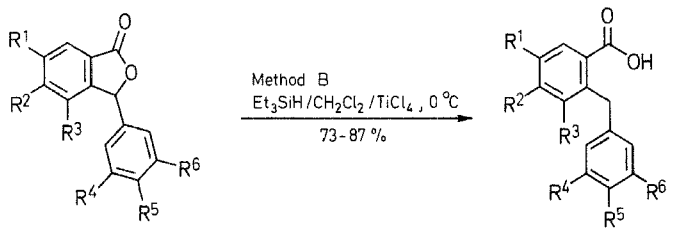
With the above strategy in mind, ionic hydrogenation of the phthalides **1** with triethylsilane/trifluoroacetic acid was attempted (see experimental, Method A), and indeed *o*-benzylbenzoic acids **2** were obtained in good yield in five cases **(a, b, e, f, g)**, including those where hydrogenolysis had failed or proceeded in poor yield.

Surprisingly, however, in the case of **1c, d** and **h**, the ionic hydrogenation with trifluoroacetic acid did not succeed. As a modification the reaction was carried out with titanium tetrachloride replacing trifluoroacetic acid[5] (Method B). This combination indeed gives the desired products **(2)** in all cases (**1a** to **1h**). The yields are good and reproducible and, more importantly, the reaction period is considerably shortened (from 24 h to 4 h). The results are presented in the Table. Investigations on further aspects of this reagent are under progress.

Table. Preparation of *o*-Benzylbenzoic Acids **2**

Product	Reaction Time (h)		Yield[a] (%)		m.p. (°C)[b] (Solvent)	Molecular Formula[c] or Lit. m.p. (°C)	IR (nujol)[d] ν(cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[e,f] δ, J(Hz)
	Method (A)	(B)	Method (A)	(B)				
2a	24	3	85	87	168 (hexane/EtOAc)	$C_{17}H_{18}O_5$ (302.3)	3450–2500, 1700	3.7, 3.75, 3.85 (3s, 9H); 4.35 (s, 2H); 6.55 (s, 1H); 6.7 (d, 2H, J = 7); 7.0 (d, 2H, J = 7); 7.5 (s, 1H)
2b	24	3	67	82	159 (hexane/EtOAc)	$C_{18}H_{20}O_6$ (332.4)	3500–2550, 1700	3.85, 3.95 (2s, 12H); 4.35 (s, 2H); 6.7–7.1 (m, 4H); 7.6 (s, 1H)
2c	–[g]	5	–	78	155 ($CHCl_3$)	$C_{19}H_{22}O_7$ (362.4)	3500–2560, 1690	3.65–3.85 (5s, 15H); 4.25 (s, 2H); 6.3 (s, 2H); 6.55 (s, 1H); 7.5 (s, 1H)
2d	–[g]	6	–	73	168 ($CHCl_3$)	168[2]	3500–2510, 1690	3.8 (s, 9H); 4.3 (s, 2H); 6.0 (s, 2H); 6.4 (s, 2H); 6.55 (s, 1H); 7.55 (s, 1H)
2e	24	3	63	83	188 (EtOAc)	$C_{17}H_{16}O_6$ (316.3)	3500–2500, 1710	3.8, 3.9 (2s, 6H); 4.3 (s, 2H); 5.85 (s, 2H); 6.65 (s, 4H); 7.5 (s, 1H)
2f	18	2	80	80	126 (hexane/EtOAc)	$C_{17}H_{18}O_5$ (302.3)	3520–2500, 1700	3.85, 3.9, 4.0 (3s, 9H); 4.4 (s, 2H); 6.6–7.0 (m, 3H); 7.2 (m, 2H); 7.8 (d, 1H, J = 7)
2g	24	4	54	81	137 (CH_2Cl_2)	$C_{18}H_{20}O_6$ (332.4)	3400–2400, 1710	3.6, 3.7, 3.9 (3s, 12H); 4.4 (s, 2H); 6.6–7.1 (m, 3H); 7.25 (d, 1H, J = 7); 7.8 (d, 1H, J = 7)
2h	–[g]	5	–	73	133 ($CHCl_3$)	$C_{19}H_{22}O_7$ (362.4)	3400–2400, 1690	3.65, 3.75, 3.85 (3s, 15H); 4.4 (s, 2H); 6.4 (s, 2H); 6.8 (d, 1H, J = 8); 7.8 (d, 1H, J = 8)

[a] Yield of isolated product.
[b] Uncorrected.
[c] Satisfactory microanalyses obtained: C ±0.21, H ±0.18.
[d] Recorded on a Perkin-Elmer 337 spectrophotometer.
[e] Recorded at 90 MHz on a Perkin-Elmer R-32 spectrometer.
[f] Additional signal at δ = 10–11 due to CO_2H for all compounds.
[g] Starting material recovered.



1a-h **2a-h**

1, 2	R_1	R_2	R_3	R_4	R_5	R_6
a	OCH_3	OCH_3	H	H	OCH_3	H
b	OCH_3	OCH_3	H	OCH_3	OCH_3	H
c	OCH_3	OCH_3	H	OCH_3	OCH_3	OCH_3
d	OCH_2O		H	OCH_3	OCH_3	OCH_3
e	OCH_3	OCH_3	H	OCH_2O		H
f	H	OCH_3	OCH_3	H	OCH_3	H
g	H	OCH_3	OCH_3	OCH_3	OCH_3	H
h	H	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3

o-Benzylbenzoic Acids 2; General Procedures:

Method A: To a stirred mixture of phthalide **1a, b, e, f,** or **g** (1 mmol) and Et_3SiH (3 mmol), CF_3CO_2H (5 mmol) is added at room temperature. The resulting mixture is stirred for the period mentioned in the Table. Excess of Et_3SiH and CF_3CO_2H is removed under vacuum and water (15 mL) is added to the residue. The mixture is extracted with ether (3 × 15 mL) and the combined ether extraxct is extracted with saturated $NaHCO_3$ solution (3 × 10 mL). The combined $NaHCO_3$ extract is acidified with 2 normal HCl and extracted with ether (3 × 15 mL). The ether extract, after drying (Na_2SO_4) and evaporation, gives the acids **2a, b, e, f** or **g**.

Method B:To a cooled (0 °C) and stirred solution of phthalide **1** (1 mmol) and Et_3SiH (3 mmol) in CH_2Cl_2 (1 mL), a solution of $TiCl_4$ (0.2 mL) in CH_2Cl_2 (1 mL) is added dropwise. The homogeneous brick red solution is stirred for the time mentioned in the Table. The excess Et_3SiH is removed under vacuum and water (15 mL) is added to residue. The resultant mixture is worked up as in Method A to give the acids **2**.

We thank CSIR, New Delhi, for an SRF award to RRJ, and DST, New Delhi, for funds.

Received: 15 December 1986; revised: 28 April 1987

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