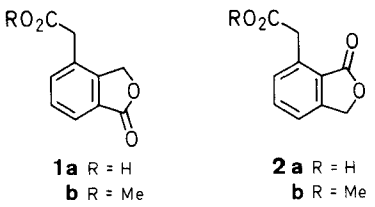
Convenient Syntheses of 1,3-Dihydro-1-oxo-4-isobenzofurancarboxylic Acid, 1,3-Dihydro-3-oxo-4-isobenzofurancarboxylic Acid, and the Homologous Acetic Acids

Richard W. Skeean, O.P. Goel*

Parke-Davis Pharmaceutical Research Division, Warner-Lambert, Company, Ann Arbor, MI 48105, USA

1-Dihydro-1-oxo- and 1,3-dihydro-3-oxo-4-isobenzofurancarboxylic acids were prepared in good yield by extensions of the Davies and Perkin synthesis of phthalide and were homologated to the corresponding acetic acid derivatives via the Arndt-Eistert reaction.

For the synthesis of novel kappa selective opioid receptor agonist analgesics, we required a large scale preparation of 1,3-dihydro-1-oxo-4-isobenzofuranacetic acid (**1a**) and the corresponding 3-isomer **2a**.

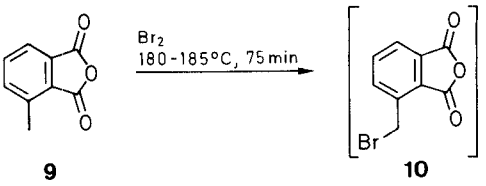


1a R = H
b R = Me

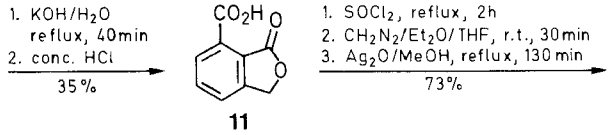
2a R = H
b R = Me

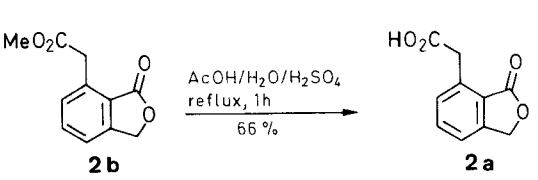
Compounds **1b** and **2b** were prepared by Arndt–Eistert homologation of the carboxylic acids **8a** and **11**.[1] However, the preparation[1] of **8a** and **11** by reduction of 1,2,3-benzenetricarboxylic acid 1,2-anhydride and separation of isomers gave less than 15% yield. This prompted us to explore alternative, more efficient, syntheses of **8a** and **11** based on the preparation of phthalide as described by Davies and Perkin.[2] Bromination of the diacid dichloride **6** at 180°C, followed by quenching in methanol, gave the dimethyl diester **7** in 60% yield. Heating **7** at 240°C extruded methyl bromide to yield **8b**. It was simpler, however, to hydrolyze **7** with aqueous potassium hydroxide, and then acidify to obtain **8a** directly in 74% yield. In conjunction with the synthesis of **8**, we prepared the dinitrile **4** in 78% yield by treatment with copper(I) cyanide in *N*-methylpyrrolidone, Newman and Boden[3] reaction conditions for the preparation of other aryl nitriles. This is an improvement over literature procedures, which start with either 2-chloro-6-nitrotoluene[4] or isophthalonitrile.[5]

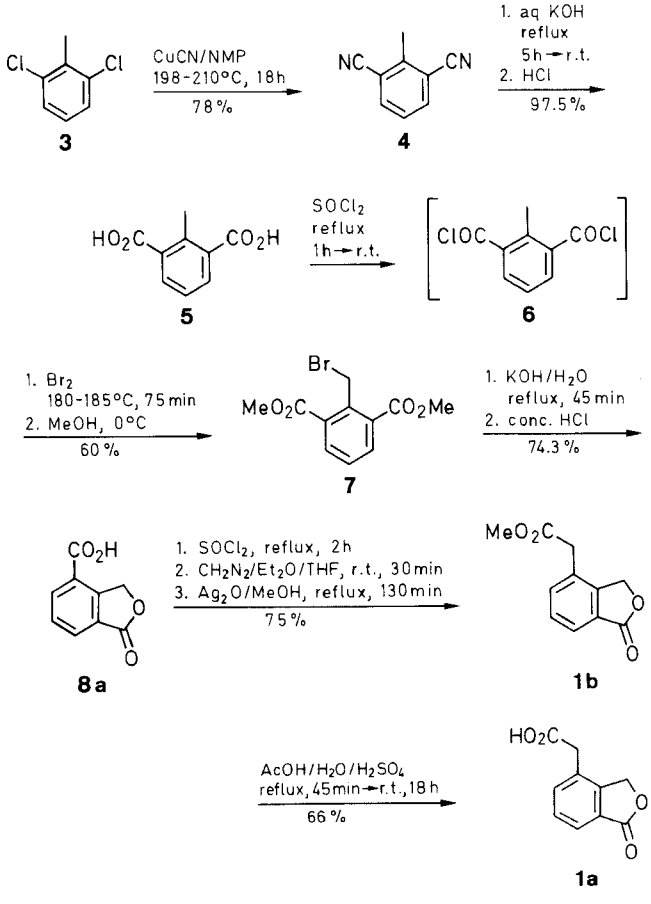
A modified procedure was used to prepare **11**. The anhydride **9** was prepared from 2-methylfuran and maleic anhydride[6] and was brominated at 180°C. The crude product **10** was hydrolyzed with aqueous potassium hydroxide and acidified to give **11** in an overall yield of 35%.



9 **10**

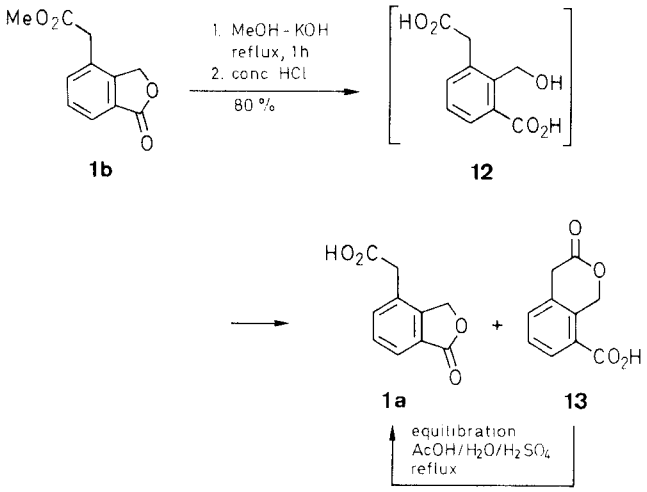






Arndt–Eistert homologation of **8a** and **11** gave **1b** and **2b**, respectively.[1] The corresponding carboxylic acids **1a** and **2a** were obtained by acid hydrolysis (Method A). However if **1b** was first saponified with methanolic KOH, and the product is isolated after acidification (Method B), a mixture of **1a** and the isomeric 3,4-dihydro-3-oxo-2-benzopyran-5-carboxylic acid (**13**) was obtained as shown by ^{1}H-NMR spectroscopic data. Apparently, lactonization of 3-carboxy-2-hydroxymethyl-1-benzeneacetic acid **12** to **13** competes kinetically with cyclization to give **1a**.

When the mixture of **1a** and **13** was subjected to equilibrating conditions (acetic acid water sulfuric acid, reflux), it was converted completely to **1a**. In practice it was simpler to subject the esters **1b** and **2b** to the aqueous acid mixture as described above and obtain the acids **1a** and **2a** directly upon cooling.



In summary, we have described improved preparative scale syntheses of **1**, **2**, **8**, and **11**, as well as the potentially useful intermediate **4**.

Melting points were obtained on a Thomas Hoover apparatus and are uncorrected. IR spectra were obtained on a Nicolet MX-1 FTIR spectrophotometer; ^{1}H-NMR spectra on a Varian XL-200 FTNMR spectrometer. Reagents and solvents were supplied by the Aldrich Chemical Co. or the MCB Co. and were used as received. GC were carried out on a Varian 6000 instrument using a 30 meter DB-5 capillary column, I.D. 0.25 mm, film thickness 0.25 µm. HPLC were obtained on a Spectra-Physics instrument with a Chromatopac C-R3a recorder-integrator, UV dectector at λ 254, an Altex ultrasphere 5 µ, C18, 25 cm column, and a mobile phase of 55% pH 2.6 phosphate buffer, 22.5% MeCN and 22.5% MeOH.

2-Methyl-1,3-benzenedicarbonitrile (4):
A 1 L 3-neck round-bottom flask equipped with a thermometer, overhead stirrer, and reflux condenser is charged with *N*-methylpyrrolidinone (300 mL), 2,6-dichlorotoluene (**3**; 120 g, 0.745 mol), and CuCN (231 g, 2.60 mol). Under N_2, the pasty mixture is stirred and heated to reflux (initially 198 °C, climbing slowly to 210 °C). The mixture is refluxed 18 h, then cooled to ~ 120 °C. The solution is poured on ice (1 kg) containing NaCN (260 g, 5.30 mol) with stirring (***caution!*** toxic fumes). The mixture is stirred for 30 min, then filtered with suction. The filter cake is washed with warm (~ 50 °C) H_2O (3 × 200 mL), then air dried. The dried product is slurried in hot MeOH (1.5 L). The methanol solution is filtered and concentrated to ~ 200 mL volume. The resulting precipitate is collected and air dried to give **4** sufficiently pure for conversion to **5**; yield: 83 g (78%); mp 132–135 °C (Lit.[4] mp 134–135 °C). A portion is sublimed to give an analytical sample, mp 134–136 °C.

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.7 (s, 3 H), 7.4 (t, 1 H, J = 8 Hz), 7.8 (d, 2 H, J = 8 Hz).

2-Methyl-1,3-benzenedicarboxylic Acid (5):
Dinitrile **4** (50.0 g, 0.351 mol) is suspended in 20% aq KOH (520 g). The mixture is stirred and refluxed for 5 h, then cooled to r.t. The solution is filtered, then acidified with conc. HCl. The precipitate is collected and washed with H_2O (3 × 100 mL), and dried in a vacuum oven at 60 °C; yield: 61.8 g (98%); mp 238–240 °C (Lit. mp 228–230 °C,[4] 245–248 °C[1]).

^{1}H-NMR (DMSO-d_6/TMS): δ = 2.6 (s, 3 H), 7.3 (t, 1 H, J = 8 Hz), 7.8 (d, 2 H, J = 8 Hz).

Dimethyl 2-(Bromomethyl)-1,3-benzenedicarboxylate (7):
The diacid **5** (46.4 g, 0.258 mol) is suspended in $SOCl_2$ (87 mL) in a 500 mL 3-neck round-bottom flask equipped with magnetic stirrer and reflux condenser topped with a N_2 blanket adapter. The mixture is stirred and refluxed for 1 h, then the excess $SOCl_2$ is removed under reduced pressure at r.t. The flask is then equipped with an addition funnel modified with a Teflon® tube reaching under the surface of the reaction mixture, and heated in an oil bath to 180–185 °C. Br_2 (18 mL, 52.7 g, 0.33 mol) is added dropwise with stirring over 75 min via the funnel. HBr and unreacted Br_2 are vented from the top of the condenser during addition of Br_2 and during 15 min of additional stirring at 180–185 °C. The mixture is then cooled to 30–40 °C and poured carefully into cold MeOH (300 mL), stirring in an ice bath. After stirring for 30 min, the precipitate is collected and washed with cold MeOH (3 × 30 mL) and then dried on the suction funnel for 20 min to give **7**; yield: 44 g (60%).

^{1}H-NMR ($CDCl_3$/TMS): δ = 3.9 (s, 6 H), 5.3 (s, 2 H), 7.3 (t, 1 H, J = 8 Hz), 7.9 (d, 2 H, J = 8 Hz).

A GC of the material shows two peaks corresponding to **7** and its pyrolysis product **8b**. The two peaks totalled > 97%. The product **7** is a *strong lachrymator* and is used directly without further characterization.

1,3-Dihydro-1-oxo-4-isobenzofurancarboxylic Acid (8a):
The diester **7** (48.4 g, 0.169 mol) is stirred and refluxed in a solution of KOH (29 g, 0.44 mol) in H_2O (250 mL) for 45 min. The mixture is cooled to ~ 40 °C and filtered. The filtrate is stirred with ice (~ 250 g) and acidified with conc. HCl. The precipitate is collected, washed with H_2O (3 × 100 mL), and dried. The crude product is recrystallized from MeOH (250 mL) to give **8a**; yield: 22.3 g (74%); mp 240–245 °C, with crystal structure change at ~ 220 °C (Lit.[1] mp 246–247 °C with crystal structure changes at ~ 180 °C and 200 °C).
^{1}H-NMR (DMSO-d_6/TMS): δ = 5.63 (s, 2 H), 7.75 (t, 1 H, J = 7 Hz), 8.11 (d, 1 H, J = 7 Hz), 8.27 (d, 1 H, J = 7 Hz).

Methyl 1,3-Dihydro-1-oxo-4-isobenzofuranacetate (1b):
Compound **8a** (10.0 g, 0.0561 mol) is refluxed for 2 h with $SOCl_2$ (55 mL). Excess $SOCl_2$ is removed under reduced pressure and the residue is taken up in anhydrous THF (200 mL, from a freshly opened bottle). This is added in small portions over a 5 min period to a solution of CH_2N_2 (~ 9 g, prepared from 65 g Diazald® according to directions supplied by the Aldrich Chemical Co. for EtOH-free material) in Et_2O (~ 700 mL) with gentle agitation. The mixture is allowed to stand at r.t. for 30 min, then excess CH_2N_2 and Et_2O are removed under reduced pressure (*caution!*).[7] The residual diazoketone is taken up in dry MeOH (400 mL) and refluxed. Ag_2O is precipitated from a solution of $AgNO_3$ (8 g) in H_2O (100 mL) by addition of 2 N NaOH, then rinsed with H_2O several times, followed by MeOH. This is slurried in MeOH (~ 10 mL) and added in 5 portions during 70 min to the refluxing diazoketone mixture. After the final addition, heating is continued for 60 min, then the mixture is cooled to r.t. and filtered. The solvent is removed on a rotary evaporator. The residue (11.1 g) is 88% pure by GC. It is recrystallized from MeOH (25 mL) to give **1b**; yield: 8.7 g (75%); 98% pure by GC.

Although this still contains traces of silver salts, it is sufficiently pure to convert to the acid **1a**. An analytical sample is prepared by dissolving 100 mg of the above product in MeOH (4 mL) and treating the solution with NaOMe (5 mg). After standing overnight, the solution is filtered and added to a solution of $NH_4H_2PO_4$ (10 mg) in H_2O (15 mL). The resulting solution is concentrated on the rotary evaporator without heat until crystals from. These are collected and dried to give **1b** (80 mg), mp 93–94 °C (Lit.[1] mp 94–95 °C).

^{1}H-NMR (DMSO-d_6/TMS): δ = 3.60 (s, 2 H), 3.67 (s, 3 H), 5.33 (s, 2 H), 7.57 (t, 1 H, J = 8 Hz), 7.67 (d, 1 H, J = 8 Hz), 7.78 (d, 1 H, J = 8 Hz).

1,3-Dihydro-1-oxo-4-isobenzofuranacetic Acid (1a):
Method A: Methyl ester **1b** (10.9 g, 0.053 mol) is added to a solution of AcOH (55 mL), H_2O (16 mL) and H_2SO_4 (2.0 mL). The mixture is refluxed 45 min, then cooled and allowed to stand at r.t. for 18 h. The product precipitates and is collected, washed with H_2O (4 × 50 mL), and dried to give **1a**; yield: 6.7 g (66%); mp 175–178 °C.

$C_{10}H_8O_4$	calc.	C 62.50	H 4.17
(192.2)	found	62.20	4.20

IR (KBr): ν = 3048, 1753, 1707, 1218, 1210, 1027, 754 cm^{-1}.

^{1}H-NMR (DMSO-d_6/TMS): δ = 3.7 (s, 2H), 5.4 (s, 2H), 7.4–7.9 (m, 3H).

Concentrating the mother liquor almost to dryness and triturating with H_2O (200 mL) gives a second crop (2.5 g); mp 170–175 °C.

Method B: A solution of ester **1b** (7.60 g, 0.037 m) in MeOH (80 mL) containing KOH (4.6 g, 0.08 m) is refluxed for 1 h. The mixture is cooled to r.t., filtered to remove some insoluble material, and concentrated to an oil. The residual oil is dissolved in H_2O (100 mL), and acidified with conc. HCl to yield an oil which later solidifies. The product is collected, redissolved in aq KOH, and acidified again to give a solid; yield 5.65 g (80%). HPLC shows this to be a mixture of two products (ratio 2:1) t_R = 5.7 and 6.2 min. The former corresponds to **1a** (obtained by Method A). ^{1}H-NMR (DMSO-d_6/TMS) of this mixture shows the expected absorptions for **1a** and additional smaller absorptions at δ = 3.4 (s) and 5.9 (s). When this mixture is subjected to the acidic conditions described in Method A, the smaller absorptions disappear and the product is identical with **1a**.

1,3-Dihydro-3-oxo-4-isobenzofurancarboxylic Acid (11):
The anhydride **9** (31.0 g, 0.190 mol, mp 115–116 °C), is treated with Br_2 (13.0 mL, 38.1 g, 0.238 mol) using the procedure described above for **7**. The mixture is cooled and mixed with H_2O (200 mL). The aq mixture is treated with sufficient KOH (~ 35 g) to render it strongly basic, then refluxed for 40 min. The mixture is cooled to 10 °C and acidified with HCl. The precipitate is collected and dried to give 18.3 g of crude product. This is recrystallized from MeOH (250 mL) to give **11**; yield: 12.0 g (35%); mp 168–171 °C (Lit.[1] mp 170–172 °C).

^{1}H-NMR (DMSO-d_6/TMS): δ = 5.46 (s, 2H), 7.48–8.17 (m, 3H).

Methyl 1,3-Dihydro-3-oxo-4-isobenzofuranacetate (2b):
Carboxylic acid **11** (10.0 g, 0.056 mol) is subjected to the Arndt–Eistert procedure as described for **8a** above. The crude product is recrystallized from EtOAc/heptane to give 8.5 g (73%) of material sufficiently pure for conversion to **2a**. An analytical sample is prepared by chromatography over silica gel with EtOAc/hexane (1:10) to give **2b**; mp 93–95 °C (Lit.[1] mp 94–96 °C).

^{1}H-NMR (DMSO-d_6/TMS): δ = 3.61 (s, 3H), 4.11 (s, 2H), 5.40 (s, 2H), 7.44 (d, 1H, J = 7 Hz), 7.57 (d, 1H, J = 7 Hz), 7.72 (t, 1H, J = 7 Hz).

1,3-Dihydro-3-oxo-4-isobenzofuranacetic Acid (2a):
Methyl ester **2b** (6.0 g, 0.29 mol) is refluxed with AcOH (18 mL), H_2O (6 mL) and H_2SO_4 (0.3 mL) for 1 h. The mixture is cooled to 0 °C. The precipitate is collected, washed with H_2O, and dried to give **2a**; yield: 3.7 g (66%); 96% pure by HPLC. An analytical sample is prepared by recrystallization from AcOH/H_2O (1:1); mp 170–173 °C.

$C_{10}H_8O_4$	calc.	C 62.50	H 4.20
(192.2)	found	62.21	4.24

IR (KBr): ν = 2990, 1765, 1749, 1704, 1699, 1406, 1225, 1079, 1004, 718 cm^{-1}.

^{1}H-NMR (DMSO-d_6/TMS): δ = 4.02 (s, 2H), 5.39 (s, 2H), 7.42 (d, 1H, J = 7 Hz), 7.55 (d, 1H, J = 7 Hz), 7.70 (t, 1H, J = 7 Hz).

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(5) Krizan, T.D.; Martin, J.C. *J. Org. Chem.* **1982**, *47*, 2681.
(6) Newman, M.S.; Lee, V. *J. Org. Chem.* **1977**, *42*, 1478.
(7) The diazoketone is nearly insoluble in Et_2O and may be collected by filtration with little loss in yield. We have been advised by the editors that doing this and proceeding with the Ag_2O/MeOH treatment would be safer than removing excess CH_2N_2/Et_2O under reduced pressure.