Facile Access to Novel 1,4-Dihydroxynaphthalene-2,3-dicarboximides and Heterofused Analogs

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This paper is dedicated to the memory of Geraldine C. Semple

A variety of novel 1,4-dihydroxynaphthalene-2,3-dicarboximides and heterofused analogs were prepared by a convenient one-pot base-catalyzed condensation of N-substituted succinimides with aromatic ortho diester derivatives.

Although alkylation2 and monoacylation3 of certain succinimide derivatives has been previously examined, there are no reports describing the sequential Claisen vicinal bis-condensation reaction between an aromatic ortho diester and a succinimide derivative. Herein we disclose that by application of such a protocol, a novel and experimentally convenient route to 1,4-dihydroxynaphthalene-2,3-dicarboximides and heterofused analogs of general formula I can be realized. Such fused systems may find potential application in the fields of medicinal and agricultural chemistry as well as in material sciences.

A communication by Snieckus4 described a somewhat related process which involved condensation of dimethylated N,N-diethylsuccinamide with diethyl phthalate to afford, after methylation of the intermediate dianion, a good yield of a 1,4-dimethoxynaphthalene-2,3-dicarboxamide derivative. His work, in turn, was a variant of the known condensation between phthalate esters and succinate esters which affords 1,4-dihydroxynaphthalene-2,3-dicarboxylic esters.5

Our method is straightforward and consists of the reaction of an appropriately N-substituted succinimide6 with an aromatic ortho diester (1.05 eq)7 in THF solution using 2.2 equivalents of sodium hydride as base in the presence of a catalytic amount of methanol. Refluxing the mixture and TLC monitoring led, after extractive workup and acidification, to the products of general formula I in unoptimized yields of 28–92%.

As shown in Table 1 and by compounds 12–14, an interesting range of naphthalene-based derivatives 1–8 can be rapidly assembled using this methodology. Novel heterocyclic variants can be produced as shown by entries 9–14. Use of four equivalents of sodium hydride or changing the base to LDA failed to significantly improve the yields. In addition, use of two equivalents of ortho diester substrate had little effect on the yield (cf. ref. 5). Ethyl or methyl esters appeared to produce comparable yields of products.

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<th>Entry</th>
<th>X</th>
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<th>R2</th>
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A limitation of the method was realized when we attempted to condense N-methyl- or N-phenylsuccinimide with 1,2-dimethylcyclohex-1-enedicarboxylate. Analysis of the crude reaction mixture by NMR, MS, and TLC suggested that the desired product 15 was formed in ca. 40% yield. Unfortunately, the product was difficult to purify chromatographically due to heavy contamination by fully aromatized byproducts. Such byproducts possibly arose through a disproportionation process.

![Chemical structures](image_url)
It is interesting to note that monoacylated intermediates were not isolated or even chromatographically detected. Such species would presumably be formed early on in the reaction pathway. Furthermore, unlike the products derived from succinate esters and succinamides, the products described herein are not susceptible to air oxidation. The attempted oxidation of I to quinone-imide II under a variety of well-established conditions was unsuccessful. This lack of reactivity is perhaps due to some electronically unfavorable interactions and/or to the intrinsically high strain which would exist in such a product.

In conclusion, we have described a very convenient, novel method to produce 1,4-dihydroxynaphthalene-2,3-dicarboximide derivatives by a facile, one-pot process. Furthermore, the synthesis of such systems by conventional means, starting with a succinate ester, would involve a multistep process, assuming that the required intermediate α-hydroxy acids would not undergo decarboxylation! This new and convenient methodology may find application in the synthesis of both natural and unnatural products.

All new compounds prepared were characterized by 1H NMR, IR, high and/or low resolution mass spectra, and elemental analysis. All reactions were run under a positive pressure of dry N2. All solvents were anhyd and were purchased from Aldrich. 1H NMR spectra were obtained on a Bruker WM-400 spectrometer operating at 400 MHz, using TMS as the internal standard. IR spectra were recorded on either Perkin-Elmer Model 727 or 1600 Series FT infrared spectrometers. HRMS (70 eV) were obtained on a Finnigan/MAT Model 95 spectrometer. All melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus. All reported values are uncorrected and are in degrees Centigrade (°C). The elemental microanalyses and mass spectra determinations were performed by the Conoco/Du Pont analytical chemistry department. Thin layer chromatography was performed using Merck silica gel 60 F254 plates. Visualization was effected with UV and/or phosphomolydbic acid.

Condensation of N-Substituted Succinimides with Aromatic ortho-Diesters: General Procedure:

Under a N2 atmosphere, NaH (0.88 g of 60 % oil dispersion, 0.53 g, 0.022 mol) was added in 4 portions over 10 min to a solution of N-substituted succinimide (0.01 mol) and aromatic ortho-diester (0.0105 mol) in anhyd THF (20 mL) containing anhyd MeOH (0.3 mL). After the ensuing mildly exothermic reaction was complete, the mixture was refluxed for 8–10 h. Progress was monitored by TLC analysis (silica gel; EtOAc, hexane mixtures). Solvent was removed in vacuo, and 6 M HCl (50 mL) was added to the residue with cooling. Et2O (50 mL) was added and the resulting heterogeneous mixture was rapidly stirred at 0°C for 20 min. Filtration, washing with Et2O followed by H2O and vacuum drying at 50°C overnight afforded essentially pure products 1–14. Analytical samples were prepared by recrystallization from dioxane. All new products except the dimethyl ether derivatives described below gave a positive FeCl3 test.

4,9-Dihydroxy-2-methyl-1H-benz[f]isoindole-1,3(2H)-dione (I):

mp 275–277°C, C13H12NO4; elemental analysis: C, H, N.
HRMS: m/z = 243.0540 ± 0.0025; calc. m/z, 243.0532.
IR (KBr): ν = 3430, 1743, 1686, 1629, 1606 cm⁻¹.
1H NMR (DMSO-d6): δ = 3.02 (s, 3H), 7.75 (dd, 2H, J = 6.4, 3.4 Hz), 8.31 (m, 2H), 10.41 (s, 2H, exchanged with D2O).
5-Fluoro-4,9-dihydroxy-2-methyl-1H-benz[f]isoindole-1,3(2H)-dione (2):

mp 266°C, C13H14FNO4; elemental analysis: C, H, N.
HRMS: m/z = 261.0421 ± 0.0025; calc. m/z, 261.0437.
IR (KBr): ν = 3430, 1743, 1673, 1640, 1611 cm⁻¹.
1H NMR (DMSO-d6): δ = 3.02 (s, 3H), 7.51 (dd, 1H, J = 7.6, 0.8 Hz), 8.15 (d, 1H, J = 8.3 Hz), 9.92 (s, 1H, exchanged with D2O), 10.71 (s, 1H, exchanged with D2O).
6,7-Dichloro-4,9-dihydroxy-2-methyl-1H-benz[f]isoindole-1,3(2H)-dione (3):

mp > 300°C, C13H9Cl2NO4; elemental analysis: C, H, N.
HRMS: m/z = 310.9765 ± 0.0031; calc. m/z, 310.9752.
IR (KBr): ν = 3094, 1749, 1678, 1645, 1635, 1588 cm⁻¹.
1H NMR (DMSO-d6): δ = 3.01 (s, 3H), 8.45 (s, 2H), 11.87 (s, 2H, exchanged with D2O).
Due to poor solubility characteristics, compound 3 was converted to the dimethyl ether derivative (excess Mel, K2CO3, MeCN, reflux, 73%), mp 264–266°C.
HRMS: m/z = 339.0060 ± 0.0033; calc. m/z, 339.0065.
IR (KBr): ν = 2942, 1761, 1703 cm⁻¹.
1H NMR (CDCl3): δ = 3.20 (s, 3H), 4.32 (s, 6H), 8.43 (s, 2H).
4,9-Dihydroxy-6-methoxy-2-methyl-1H-benz[f]isoindole-1,3(2H)-dione (4):

mp 282–284°C, C13H14NO5; elemental analysis: C, H, N.
HRMS: m/z = 273.0640 ± 0.0027; calc. m/z, 273.0537.
IR (KBr): ν = 3443, 1743, 1688, 1673, 1630, 1612 cm⁻¹.
1H NMR (DMSO-d6): δ = 3.06 (s, 3H), 3.98 (s, 3H), 7.40 (dd, 1H, J = 9.1, 1.5 Hz), 7.70 (d, 1H, J = 2.1 Hz), 8.26 (dd, 1H, J = 9.1, 1.5 Hz), 10.37 (s, 2H, exchanged with D2O).
4,9-Dihydroxy-6-methoxy-1H-benz[f]isoindole-1,3(2H)-dione (5):

mp > 300°C, C14H15NO5; elemental analysis: C, H, N.
HRMS: m/z = 257.0670 ± 0.0026; calc. m/z, 257.0688.
IR (KBr): ν = 3433, 1744, 1679, 1627, 1616 cm⁻¹.
1H NMR (DMSO-d6): δ = 2.52 (s, 3H), 3.01 (s, 3H), 7.57 (d, 1H, J = 8.5 Hz), 8.09 (s, 1H), 8.20 (d, 1H, J = 8.5 Hz), 10.30 (s, 1H, exchanged with D2O), 10.34 (s, 1H, exchanged with D2O).
4,9-Dihydroxy-8-methyl-2-phenyl-1H-benz[f]isoindole-1,3(2H)-dione (6):

mp 268–270°C, C34H29NO4/1/2H2O; elemental analysis: C, H, N.
HRMS: m/z = 319.0824 ± 0.0032; calc. m/z, 319.0845.
IR (KBr): ν = 3408, 1740, 1694, 1653, 1638, 1590 cm⁻¹.
1H NMR (DMSO-d6): δ = 2.55 (s, 3H), 7.44 (m, 3H), 7.62 (d, 1H, J = 8.3 Hz), 8.16 (s, 1H), 8.26 (d, 1H, J = 8.3 Hz), 10.46 (s, 1H, exchanged with D2O), 10.50 (s, 1H, exchanged with D2O).
2-Cyclohexyl-4,9-dihydroxy-6-methoxy-1H-benz[f]isoindole-1,3(2H)-dione (7):

mp 248–249°C, C31H29NO5; elemental analysis: C, H, N.
HRMS: m/z = 341.1270 ± 0.0034; calc. m/z, 341.1263.
IR (KBr): ν = 3429, 2924, 1733, 1671, 1635, 1614 cm⁻¹.
1H NMR (DMSO-d6): δ = 1.14–1.23 (m, 1H), 1.33 (m, 2H), 1.67 (m, 3H), 1.82 (m, 2H), 2.14 (m, 2H), 3.93 (s, 3H), 3.98 (m, 1H), 7.35 (dd, 1H, J = 9.1, 2.6 Hz), 7.64 (d, 1H, J = 2.3 Hz), 8.22 (d, 1H, J = 9.1 Hz), 10.27 (s, 2H, exchanged with D2O).
6,7-Dichloro-2-(3,5-dichlorophenyl)-4,9-dihydroxy-1H-benz[f]isoindole-1,3(2H)-dione (8):

mp > 300°C, C18H16Cl4NO4; elemental analysis: C, H, N.
HRMS: m/z = 440.9133 ± 0.0044; calc. m/z, 440.9129.
IR (KBr): ν = 3403, 1741, 1685, 1634, 1617 cm⁻¹.

Due to poor solubility characteristics, we were unable to obtain an
¹H NMR spectrum of compound 8. Therefore, it was converted to
the dimethyl ether derivative (excess Me₃C=O, CH₃CN, reflux,
81%), mp > 300°.

C₃₇H₅₂Cl₂NO₄: DCl/MS (Cl₃H₇) HI: M⁺ 472.
IR (KBr): ˌν = 1753, 1713, 1589 cm⁻¹.

¹H NMR (DMSO- d₆): δ = 4.24 (s, 6 H), 7.64 (s, 2 H), 7.78 (s, 1 H),
8.57 (d, 2 H, J = 3.1 Hz).

7-(3,5-Dichlorophenyl)-5,9-dihydroxy-1H-pyrrrolo[3,4-g]quinoline-6,8(7H)-dione (9):

mp 289–292°C. C₁₇H₁₁Cl₂N₂O₄: elemental analysis: C, H, N.
HRMS: m/z = 373.9840 ± 0.0037; calc. m/z 373.9861.
IR (KBr): ν = 3370, 3332, 1753, 1690 cm⁻¹.

¹H NMR (DMSO- d₆): δ = 7.02–7.80 (br m, 5 H), 8.30–8.95 (br m,
2 H), 9.05–9.45 (br m, 1 H); signals appeared as a series of broad
peaks due to very poor sample solubility.

7-Cyclohexyl-5,9-dihydroxy-1H-pyrrrolo[3,4-g]quinoline-6,8(7H)-dione (10):

mp > 300°C. C₁₇H₁₈N₂O₄: elemental analysis: C, H, N.
HRMS: m/z = 312.1109 ± 0.0031; calc. m/z 312.1110.
IR (KBr): ν = 3400, 1750, 1690 cm⁻¹.

¹H NMR (DMSO- d₆): δ = 1.10–1.40 (m, 3 H), 1.65 (m, 3 H), 1.70
(m, 2 H), 2.11 (m, 2 H), 3.57 (m, 1 H), 7.76 (dd, 1 H, J = 8.3, 3.9 Hz),
8.68 (d, 1 H, J = 8.3 Hz), 9.01 (d, 1 H, J = 3.9 Hz), 10.67 (s, 2 H,
exchanged with D₂O).

5,9-Dihydroxy-7-methyl-1H-pyrrolo[3,4-g]quinoline-6,8(7H)-dione (11):

mp 291–292°C. C₁₂H₁₃N₂O₄: elemental analysis: C, H, N.
HRMS: m/z = 244.0815 ± 0.0025; calc. m/z 244.0848.
IR (KBr): ˌν = 3375, 3288, 1752, 1696, 1660, 1634 cm⁻¹.

¹H NMR (DMSO- d₆): δ = 3.01 (s, 3 H), 7.79 (dd, 1 H, J = 8.4,
4.2, 1.5 Hz), 8.72 (dd, 1 H, J = 8.4, 1.5 Hz), 9.04 (dd, 1 H, J = 4.3,
1.5 Hz), 10.67 (br s, 1 H, exchanged with D₂O).

4,9-Dihydroxy-2-methyl-1H-pyrrolo[3,4-g]isoquinoline-1,3(2H)-dione (12):

mp > 300°C. C₁₄H₁₄N₂O₄: elemental analysis gave poor carbon
results even after repeated purifications/recrystallizations.
HRMS: m/z = 244.0847 ± 0.0025; calc. m/z 244.0848.
IR (KBr): ν = 3366, 1748, 1689, 1654, 1624, 1613 cm⁻¹.

¹H NMR (D₂O, TSP): δ = 3.01 (s, 3 H), 8.57 (m, 1 H), 8.62 (m,
1 H), 9.68 (s, 1 H).

4,8-Dihydroxy-6-methyl-5H-furo[3,4-f]isoindole-5,7(6H)-dione (13):

mp 282°C (dcv). C₁₄H₁₄N₂O₄: elemental analysis: C, H, N.
HRMS: m/z = 233.0345 ± 0.0025; calc. m/z 233.0324.
IR (KBr): ˌν = 3208, 1741, 1708, 1666, 1621 cm⁻¹.

¹H NMR (DMSO- d₆): δ = 2.92 (s, 3 H), 8.58 (s, 2 H), 11.37 (s, 2 H,
exchanged with D₂O).

6-Cyclohexyl-4,8-dihydroxy-5H-thieno[2,3-f]isoindole-5,7(6H)-dione (14):

mp 250–251°C. C₁₈H₁₄N₂O₄S: elemental analysis: C, H, N.
HRMS: m/z = 317.0706 ± 0.0031; calc. m/z 317.0722.
IR (KBr): ν = 3104, 3078, 1736, 1670, 1609 cm⁻¹.

¹H NMR (DMSO- d₆): δ = 1.06–1.22 (m, 1 H), 1.32 (m, 2 H), 1.66
(m, 3 H), 1.81 (m, 2 H), 2.10 (m, 2 H), 3.94 (m, 1 H), 7.74 (d, 1 H,
J = 5.5 Hz), 7.95 (d, 1 H, J = 5.5 Hz), 10.40 (br s, 1 H, exchanged
with D₂O), 10.65 (br s, 1 H, exchanged with D₂O).

JES thanks Dr. J. W. O’Boogie for continued inspiration and G.M. Semple for tea and sympathy.

(1) New address: Corvas International, Inc; 3030 Science Park
Road; San Diego, CA 92121.

1987, 1679.


(5) Application of the succinate-phthalate ester condensation in
Fredericamycin A total synthesis: Kelly, T. R.; Bell, S. H.;
Ohashi, N.; Armstrong-Chong, R. J. J. Am. Chem. Soc. 1988,
110, 6471.


(7) N-Substituted succinimides were either commercially available
or were prepared by refluxing an equimolar mixture of succinic
anhydride and primary amine in HOAc (1 M, soln., ca. 24 h
reaction time). After cooling and dilution with ice-water, solids
were collected, dried and recrystallized from the appropriate
solvent.

(8) NaHCO₃ (0°C to reflux). Dimethyl 2,3-pyridinedicarboxylate, mp
53–55°C, was prepared from quinolinic anhydride: (a) NaH, heat;
(b) SOCl₂ (0°C to reflux); (c) NaHCO₃, 81%. Dimethyl 3,4-pyridine-
dicarboxylate, yellow oil, was prepared from cichemonic acid:
(a) 2 equiv 1,1-carbonyldimidazole, MeCN, r.t. (b) MeOH, r.t.
reflux, 73%. Dimethyl 2,3-thiophenedicarboxylate, mp 30–32°C,
was prepared from thiophene-3-carboxylic acid: (a) BuLi, THF,
–78°C; (b) CO₂, –78°C to r.t.; (c) HCl, 0°C, 80%; (d) MeOH, SOCl₂,
reflux, 84%.

We attempted this oxidation under the following conditions:
(a) 5% FeCl₃ in EtOH, r.t. to reflux; (b) (NH₄)₂Ce(NO₃)₆, CH₃CN, H₂O,
20°C, 3 min. This reagent gave a 45% yield of the quinhydrone
complex, bright orange solid, mp 290–292°C. Further attempted
oxidations with CAN under a variety of conditions failed to produce II. (c) Jones’ Reagent,
acetone, 0°C to r.t., 12 h; (d) Pb(OAc)₄, C₆H₆, reflux, 15 h.