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

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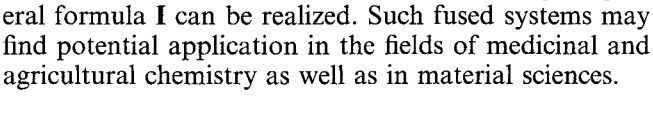
This paper is dedicated to the memory of Geraldine C. Semple

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

Although alkylation[2] and monoacylation[3] 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 experimentially 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.



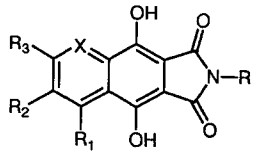
I

A communication by Snieckus[4] described a somewhat related process which involved condensation of dimetalated *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 succinimide[6] 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%.

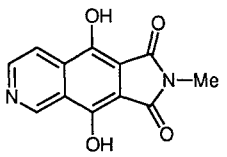
As shown in Table 1 and by compounds **12–14**, an interesting range of naphthalene-based derivatives **1–8** can be rapidly assembled using this methodology. Novel heterocyclic variants can be produced as shown by entries **9–14**. Use of four equivalents of sodium hydride or changing the base to LDA 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.

Table 1. (8-Aza)-1,4-dihydroxynaphthalene-2,3-dicarboximides **I**

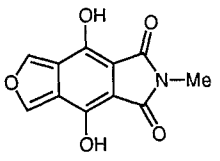


Entry	X	R	R_1	R_2	R_3	Yield (%)
1	CH	Me	H	H	H	40
2	CH	Me	F	H	H	48
3	CH	Me	H	Cl	Cl	82
4	CH	Me	H	MeO	H	68
5	CH	Me	H	Me	H	70
6	CH	Ph	H	Me	H	28
7	CH	Cyclohexyl	H	MeO	H	61
8	CH	3,5-Cl_2Ph	H	Cl	Cl	31
9	N	3,5-Cl_2Ph	H	H	H	76
10	N	Cyclohexyl	H	H	H	72
11	N	Me	H	H	H	92

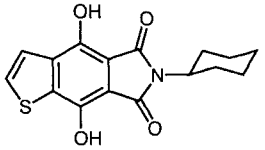
A limitation of the method was realized when we attempted to condense *N*-methyl- or *N*-phenylsuccinimide with 1,2-dimethylcyclohex-1-enedicarboxylate. Analysis of the crude reaction mixture by NMR, MS, and TLC suggested that the desired product **15** was formed in ca. 40% yield. Unfortunately, the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



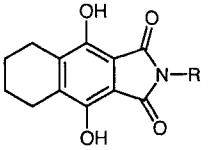
12 (27%)



13 (73%)



14 (84%)



15, *low yield*

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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[5] and succinamides,[4] the products described herein are not susceptible to air oxidation. The attempted oxidation of **1** to quinone-imide **II** under a variety of well-established conditions was unsuccessful.[8] 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.

1 **II**

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 *o*-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 ^{1}H NMR, IR, high and/or low resolution mass spectra, and elemental analysis. All reactions were run under a positive pressure of dry N_2. All solvents were anhyd and were purchased from Aldrich. All reagents were purchased from Aldrich. ^{1}H 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 F-254 plates. Visualization was effected with UV and/or phosphomolybdic acid.

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

Under a N_2 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. Et_2O (50 mL) was added and the resulting heterogeneous mixture was rapidly stirred at 0 °C for 20 min. Filtration, washing with Et_2O followed by H_2O 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 $FeCl_3$ test.

4,9-Dihydroxy-2-methyl-1H-benz[f]isoindole-1,3(2H)-dione **(1)**:
mp 275–277 °C, $C_{13}H_9NO_4$; elemental analysis: C, H, N.
HRMS: $m/z = 243.0540 \pm 0.0025$; calc. m/z, 243.0532.
IR (KBr): $\nu = 3430, 1743, 1686, 1629, 1606\ cm^{-1}$.
^{1}H NMR (DMSO-d_6): $\delta = 3.02$ (s, 3H), 7.75 (dd, 2H, $J = 6.4$, 3.4 Hz), 8.31 (m, 2H), 10.41 (s, 2H, exchanged with D_2O).

5-Fluoro-4,9-dihydroxy-2-methyl-1H-benz[f]isoindole-1,3(2H)-dione **(2)**:
mp 266 °C, $C_{13}H_8FNO_4$; elemental analysis: C, H, N.
HRMS: $m/z = 261.0421 \pm 0.0025$; calc. m/z, 261.0437.
IR (KBr): $\nu = 3430, 1743, 1673, 1640, 1611\ cm^{-1}$.
^{1}H NMR (DMSO-d_6): $\delta = 3.02$ (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 D_2O), 10.71 (s, 1H, exchanged with D_2O).

6,7-Dichloro-4,9-dihydroxy-2-methyl-1H-benz[f]isoindole-1,3(2H)-dione **(3)**:
mp > 300 °C, $C_{13}H_7Cl_2NO_4$; elemental analysis: C, H, N.
HRMS: $m/z = 310.9765 \pm 0.0031$; calc. m/z 310.9752.
IR (KBr): 3094, 1749, 1678, 1645, 1635, 1588 cm^{-1}.
^{1}H NMR (DMSO-d_6): $\delta = 3.01$ (s, 3H), 8.45 (s, 2H), 11.87 (s, 2H, exchanged with D_2O).
Due to poor solubility characteristics, compound **3** was converted to the dimethyl ether derivative (excess MeI, K_2CO_3, MeCN, reflux, 73%), mp 264–266 °C.
HRMS: $m/z = 339.0060 \pm 0.0033$; calc. m/z 339.0065.
IR (KBr): $\nu = 2942, 1761, 1703\ cm^{-1}$.
^{1}H NMR ($CDCl_3$): $\delta = 3.20$ (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, $C_{14}H_{11}NO_5$; elemental analysis: C, H, N.
HRMS: $m/z = 273.0640 \pm 0.0027$; calc. m/z 273.0637.
IR (KBr): $\nu = 3443, 1746, 1688, 1673, 1630, 1612\ cm^{-1}$.
^{1}H NMR (DMSO-d_6): $\delta = 3.06$ (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 D_2O).

4,9-Dihydroxy-2,6-dimethyl-1H-benz[f]isoindole-1,3(2H)-dione **(5)**:
mp > 300 °C, $C_{14}H_{11}NO_4$; elemental analysis: C, H, N.
HRMS: $m/z = 257.0670 \pm 0.0026$; calc. m/z 257.0688.
IR (KBr): $\nu = 3433, 1744, 1679, 1627, 1616\ cm^{-1}$.
^{1}H NMR (DMSO-d_6): $\delta = 2.52$ (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 D_2O), 10.34 (s, 1H, exchanged with D_2O).

4,9-Dihydroxy-8-methyl-2-phenyl-1H-benz[f]isoindole-1,3(2H)-dione **(6)**:
mp 268–270 °C, $C_{14}H_{11}NO_4 \cdot 1/2H_2O$; elemental analysis: C, H, N.
HRMS: $m/z = 319.0824 \pm 0.0032$; calc. m/z 319.0845.
IR (KBr): $\nu = 3408, 1740, 1694, 1653, 1638, 1590\ cm^{-1}$.
^{1}H NMR (DMSO-d_6): $\delta = 2.55$ (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 D_2O), 10.50 (s, 1H, exchanged with D_2O).

2-Cyclohexyl-4,9-dihydroxy-6-methoxy-1H-benz[f]isoindole-1,3(2H)-dione **(7)**:
mp 248–249 °C, $C_{19}H_{19}NO_5$; elemental analysis: C, H, N.
HRMS: $m/z = 341.1270 \pm 0.0034$; calc. m/z 341.1263.
IR (KBr): $\nu = 3429, 2924, 1733, 1671, 1635, 1614\ cm^{-1}$.
^{1}H NMR (DMSO-d_6): $\delta = 1.14–1.23$ (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 D_2O).

6,7-Dichloro-2-(3,5-dichlorophenyl)-4,9-dihydroxy-1H-benz[f]isoindole-1,3-(2H)-dione **(8)**:
mp > 300 °C. $C_{18}H_7Cl_4NO_4$; elemental analysis: C, H, N.
HRMS: $m/z = 440.9133 \pm 0.0044$; calc. m/z 440.9129.

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IR (KBr): $\nu = 3403, 1741, 1685, 1634, 1617\ cm^{-1}$.

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 MeI, K_2CO_3, CH_3CN, reflux, 81%), mp > 300°.

$C_{20}H_{11}Cl_4NO_4$; DCI/MS (CH_4): MH^+ 472.

IR (KBr): $\nu = 1753, 1713, 1589\ cm^{-1}$.

^1H NMR (DMSO-d_6): $\delta = 4.24$ (s, 6H), 7.64 (s, 2H), 7.78 (s, 1H), 8.57 (d, 2H, $J = 3.1$ Hz).

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

mp 289–292°C. $C_{17}H_8Cl_2N_2O_4$; elemental analysis: C, H, N.

HRMS: $m/z = 373.9840 \pm 0.0037$; calc. m/z 373.9861.

IR (KBr): $\nu = 3370, 3332, 1753, 1690\ cm^{-1}$.

^1H NMR (DMSO-d_6): $\delta = 7.02–7.80$ (br m, 5H), 8.30–8.95 (br m, 2H), 9.05–9.45 (br m, 1H); signals appeared as a series of broad peaks due to very poor sample solubility.

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

mp > 300°C. $C_{17}H_{16}N_2O_4$; elemental analysis: C, H, N.

HRMS: $m/z = 312.1109 \pm 0.0031$; calc. m/z 312.1110.

IR (KBr): $\nu = 3400, 1750, 1690\ cm^{-1}$.

^1H NMR (DMSO-d_6): $\delta = 1.10–1.40$ (m, 3H), 1.65 (m, 3H), 1.70 (m, 2H), 2.11 (m, 2H), 3.97 (m, 1H), 7.76 (dd, 1H, $J = 8.3, 3.9$ Hz), 8.68 (d, 1H, $J = 8.3$ Hz), 9.01 (d, 1H, $J = 3.9$ Hz), 10.67 (s, 2H, exchanged with D_2O).

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

mp 291–292°C, $C_{12}H_8N_2O_4$; elemental analysis: C, H, N.

HRMS: $m/z = 244.0489 \pm 0.0025$; calc. m/z 244.0484.

IR (KBr): $\nu = 3375, 3288, 1752, 1696, 1660, 1634\ cm^{-1}$.

^1H NMR (DMSO-d_6): $\delta = 3.01$ (s, 3H), 7.79 (ddd, 1H; $J = 8.4, 4.2, 1.5$ Hz), 8.72 (dd, 1H, $J = 8.4, 1.5$ Hz), 9.04 (dd, 1H, $J = 4.3, 1.5$ Hz), 10.67 (br s, 1H, exchanged with D_2O).

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

mp > 300°C, $C_{12}H_8N_2O_4$; elemental analysis gave poor carbon results even after repeated purifications/recrystallizations.

HRMS: $m/z = 244.0467 \pm 0.0025$; calc. m/z 244.0484.

IR (KBr): $\nu = 3366, 1748, 1689, 1654, 1624, 1613\ cm^{-1}$.

^1H NMR (D_2O, TSP): $\delta = 3.01$ (s, 3H), 8.57 (m, 1H), 8.62 (m, 1H), 9.68 (s, 1H).

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

mp 282°C (dec), $C_{11}H_7NO_5$; elemental analysis: C, H, N.

HRMS: $m/z = 233.0345 \pm 0.0025$; calc. m/z 233.0324.

IR (KBr): $\nu = 3208, 1741, 1708, 1666, 1623\ cm^{-1}$.

^1H NMR (DMSO-d_6): $\delta = 2.92$ (s, 3H), 8.58 (s, 2H), 11.37 (s, 2H, exchanged with D_2O).

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

mp 250–251°C, $C_{16}H_{15}NO_4S$; elemental analysis: C, H, N.

HRMS: $m/z = 317.0708 \pm 0.0031$; calc. m/z 317.0722.

IR (KBr): $\nu = 3104, 3078, 1736, 1670, 1609\ cm^{-1}$.

^1H NMR (DMSO-d_6): $\delta = 1.06–1.22$ (m, 1H), 1.32 (m, 2H), 1.66 (m, 3H), 1.81 (m, 2H), 2.10 (m, 2H), 3.94 (m, 1H), 7.74 (d, 1H, $J = 5.5$ Hz), 7.95 (d, 1H, $J = 5.5$ Hz), 10.40 (br s, 1H, exchanged with D_2O), 10.65 (br s, 1H, exchanged with D_2O).

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

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

(7) Phthalate esters were prepared by treatment of the parent dicarboxylic acids with MeOH and $SOCl_2$ (0°C to reflux). Dimethyl 2,3-pyridinedicarboxylate, mp 53–55°C, was prepared from quinolinic anhydride: (a) MeOH, heat; (b) $SOCl_2$ (0°C to reflux); (c) $NaHCO_3$, 81%. Dimethyl 3,4-pyridinedicarboxylate, yellow oil, was prepared from cinchomeronic acid: (a) 2 equiv 1,1′-carbonyldiimidazole, MeCN, r.t.; (b) MeOH, r.t. to reflux, 73%. Dimethyl 2,3-thiophenedicarboxylate, mp 30–32°C, was prepared from thiophene-3-carboxylic acid: (a) BuLi, THF, −78°C; (b) CO_2, −78°C to r.t.; (c) HCl, 0°C, 80%; (d) MeOH, $SOCl_2$, reflux, 84%.

(8) We attempted this oxidation under the following conditions: (a) 5% $FeCl_3$ in EtOH, r.t. to reflux; (b) $(NH_4)_2Ce(NO_3)_6$, CH_3CN, H_2O, 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., 12h; (d) $Pb(OAc)_4$, C_6H_6, reflux, 15h.

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