Synthesis of Functionalized Hydroxyphthalides and Their Conversion to 3-Cyano-1(3*H*)-isobenzofuranones. The Diels–Alder Reaction of Methyl 4,4-Diethoxybutynoate and Cyclohexadienes

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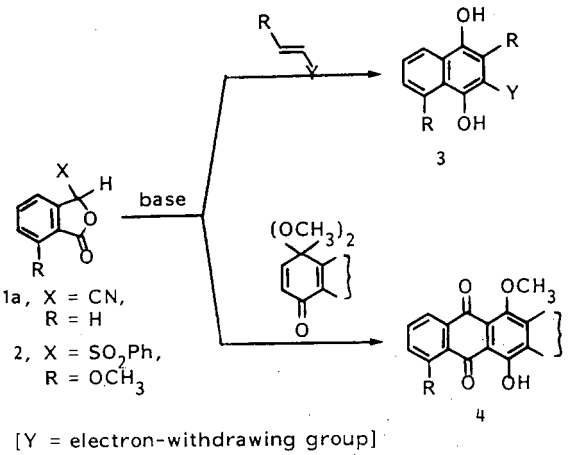
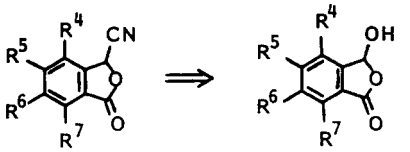
Several methods have been used in the preparation of functionalized hydroxyphthalides. Metalation of *N,N*-diethyl-3-methoxybenzamide, followed by reaction with dimethylformamide and hydrolysis, furnished 3-hydroxy-4-methoxy-1(3*H*)-isobenzofuranone in 52% yield. Reaction of the metalation product of *m*-fluorobenzaldehyde dimethyl acetal with carbon dioxide, followed by hydrolysis, gave 3-hydroxy-7-fluoro-1(3*H*)-isobenzofuranone in 86% yield. Especially noteworthy is the excellent metalation result with fluorine as a directing group. However, metalation of 2,5-dimethoxybenzaldehyde dimethyl acetal followed by reaction with carbon dioxide gave 2,5-dimethoxy-4-formylbenzoic acid (62%), not the corresponding hydroxyphthalide. The key step in the preparation of the remaining hydroxyphthalides was the Diels–Alder reaction of methyl 4,4-diethoxybutynoate with 1,3- and 1,4-cyclohexadienes, followed by in situ aromatization with loss of ethylene. Hydrolysis of the resulting products furnished functionalized hydroxyphthalides in good yields. Conversion of the above hydroxyphthalides to their corresponding 3-cyano-1(3*H*)-isobenzofuranones could not be conveniently effected by literature procedures. However, a unique procedure for cyclization of the corresponding cyanohydrins using oxalyl chloride and dimethylformamide did lead to a good preparation of the above mentioned systems.

Convergent methods for assembling tetracyclic ring systems are of interest due to synthetic efforts directed toward anthracyclinone-type antibiotics.[1] Organometallic derivatives of **1**[2] and **2**[3]—which we have termed 1,4-dipole equivalents[4]—are useful reagents for annelation of electron-deficient olefins via a sequence of Michael addition/cyclization/tautomerization (Scheme I). The reaction of **1** and **2** with simple Michael acceptors affords 1,4-dihydroxynaphthalene derivatives **3**, while reaction with quinone monoketals affords anthraquinone systems such as **4**. This latter reaction is especially efficient with **1a**[4d] as the annelating agent and has been utilized in a useful, convergent synthesis of the anthracyclinone antibiotic aglycons 4-demethoxydaunomycinone and daunomycinone.[5]

Scheme I. Illustrative Annelation Reactions of 1a and 2



We required in our studies a route to a number of substituted derivatives of **1**. Especially interesting were those compounds having the substitution pattern present in a variety of naturally occurring ring systems:[6,7a] compounds having oxygen substituents at C-7, at C-5 and C-7, and at C-4 and C-7. The corresponding hydroxyphthalide derivatives **5**, which are logical intermediates for the preparation of **1**, are not commercially available. Hydroxyphthalides have been prepared by functional-group interconversions of the corresponding phthalic anhydrides,[7a,8] phthalides,[7b,c] and *o*-methylbenzoic acid derivatives[4d] or from metalation procedures[9]; however, these methods were



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(2) (a) Kraus, G. A.; Sugimoti, H. *Tetrahedron Lett.* **1978**, 2263. (b) Li, T.; Wu, Y. *J. Am. Chem. Soc.* **1981**, *103*, 7007. (c) Keay, B. A.; Rodrigo, R. *Can. J. Chem.* **1983**, *61*, 637. (d) Kraus, G. A.; Cho, H.; Crowley, S.; Roth, B.; Sugimoto, H.; Prugh, S. *J. Org. Chem.* **1983**, *48*, 3439.

(3) For leading references, see: Hauser, F. M.; Mal, D. *J. Am. Chem. Soc.* **1983**, *105*, 5688.

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(6) Thomson, R. H. "Naturally Occurring Quinones"; Academic Press: New York, 1971; Chapter 6.

(7) (a) Taub D; Girotra, N. N.; Hoffsommer, R. D.; Kuo, C. H.; Slates, H. L.; Weber, S.; Wendler, N. L. *Tetrahedron* **1968**, *24*, 2443. (b) Uemura, M.; Tokuyama, S.; Sakan, T. *Chem. Lett.* **1975**, 1195. (c) Trost, B. M.; Rivers, G. T.; Gold, J. M. *J. Org. Chem.* **1980**, *45*, 1835.

(8) Reduction of phthalic and other cyclic anhydrides with a variety of reducing agents usually affords the corresponding phthalides: (a) Bailey, D. M.; Johnson, R. E. *J. Org. Chem.* **1970**, *35*, 3574. (b) Mellows, S. M.; Sammes, P. G. *J. Chem. Soc. D* **1971**, 21. (c) Birch, A. J.; Russell, R. A. *Aust. J. Chem.* **1971** *24*, 1975. (d) Burke, D. E.; LeQuesne, P. W. *J. Org. Chem.* **1971**, *36*, 2397. (e) Shroff, C. C.; Stewart, W. S.; Uhm, S. J.; Wheeler, J. W. *Ibid.* **1971**, *36*, 3356. (f) Koizumi, T.; Yamamoto, N.; Yoshii, E. *Chem. Pharm. Bull.* **1973**, *21*, 312. (g) Subba Rao, B. C. *Curr. Sci.* **1961**, *30*, 218. (h) McAlles, A. J.; McCrindle, R.; Sneddon, D. W. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2030, 2037.

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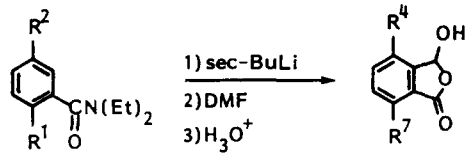
not attractive for some of the compounds required for our studies.

We report herein a convenient synthesis of a number of hydroxyphthalides by several strategies and their conversion to the corresponding 3-cyano-1(3*H*)-isobenzofuranones (1). This latter conversion is often not trivial, and detailed experimental procedures to effect this step in good yield are reported.

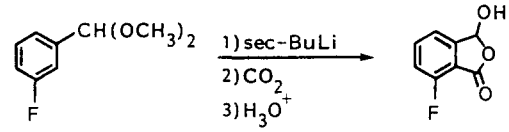
Substituted Hydroxyphthalides via Metalation Procedures. The commerical availability of the corresponding benzoic acid derivatives prompted examination of the ortho-metalation chemistry[4d,9a,b] of **6** and **7** as a route to the respective hydroxyphthalides **5b,c**. This route



6, R^1 = H, R^2 = OCH_3 5b, R^4 = OCH_3, R^7 = H (54%)
7, R^1 = F, R^2 = H 5c, R^4 = H, R^7 = F (10%)

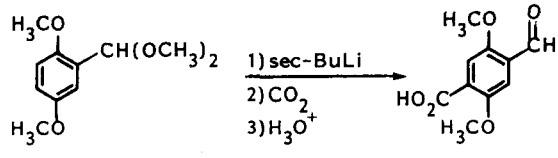
furnished **5b** in acceptable overall yield (52%) from amide **6**, but the yield of **5c** from **7** was only 10% under the best of conditions.

The ortho metalation of dimethyl acetals of aromatic aldehydes[9c] followed by their reaction with carbon dioxide and hydrolysis would afford a complementary route to hydroxyphthalides. However, the reported yields for the metalation/functionalization sequence were good for only a few selected systems.[9c] Even the doubly activated position of *m*-methoxybenzaldehyde dimethyl acetal was metalated and carbonated in only 22% yield.[9c] Interestingly, the metalation of **8** using *sec*-butyllithium in tetrahydrofuran followed by reaction with carbon dioxide and hydrolysis furnished **5c** in 86% yield. The small steric



8 5c (86%)

influence of fluorine together with its ortho-directing effect on metalation[10] may account for the excellent yield in the reaction of **8** vs. that of *m*-methoxybenzaldehyde dimethyl acetal. The limitations of the route were affirmed when metalation of **9** with *sec*-butyllithium followed by carbonation and hydrolysis did not afford the hydroxyphthalide but instead gave **10** in 62% yield.[11] The structure as-



9 10 (62%)

signment for **10** is based on spectroscopic and analytical data detailed in the Experimental Section. The regiochemical assignment appears secure since both aromatic hydrogens appear as sharp singlets at δ 7.82 and 7.49 in the ^{1}H NMR spectrum. This requires a para relationship between the hydrogens and rules out isomeric metalation products.

Substituted Hydroxyphthalides via the Diels–Alder Reaction. The restrictions on the metalation routes to hydroxyphthalides, especially for aromatic rings having competitive metalation sites, prompted examination of a better synthesis of ring-oxygenated hydroxyphthalides. A powerful method for the synthesis of highly substituted aromatic systems is the Diels–Alder reaction of activated acetylenes and 1,3-cyclohexadienes (see the Alder–Stein Rule[12]). The initially formed bicyclo[2.2.2]octadiene generally decomposes in situ to ethylene and the aromatic compound. This chemistry was utilized by Hodge and Harland[13] to prepare phthalide derivatives, and an analogous reaction here would furnish hydroxyphthalides.

The acetylene **12** was an ideal dienophile component since it possessed the correct oxidation state at the carbonyl groups for the hydroxyphthalide and both electronic and steric effects should favor regioselective reactions with oxygenated diene systems. However, somewhat suprisingly, the Diels–Alder chemistry of **12** has not been extensively studied.[14] The required acetylene **12** was synthesized in 82% yield by addition of the lithium salt of 3,3-diethoxypropyne[15] to methyl chloroformate.

Many 1,3-cyclohexadienes are available by Birch reduction of the corresponding aromatic compound to the 1,4-cyclohexadiene followed by base-catalyzed isomerization. A synthetic expedient is to perform the isomerization of the 1,4-diene to the 1,3-diene in situ either catalytically[13,16] or thermally.[17] In this work the thermal isomerization was convenient; thus, heating (160–170 °C) the dienes **11d–f** with the acetylene **12** afforded, after distillation, the respective aromatic systems **14d–f** in good yield (ca. 80%). The high regioselectivity of the reaction was apparent from the ^{13}C NMR spectra of the crude products which should have detected 10% of a regioisomeric product. Hydrolysis of **14d–f** afforded the corresponding hydroxyphthalides **5d–f** (75–79%). The hydroxyphthalide **5d** obtained from this sequence was identical with an authentic sample,[4d] thus confirming the regiochemistry of the product based on the expected Diels–Alder orientation.

The use of a more readily available 1,4-cyclohexadiene in the reaction sequence rather than the 1,3-cyclohexadiene is not acceptable in all cases. Thus, reaction of 1,5-dimethoxy-1,4-cyclohexadiene (**11g**) with acetylene **12** afforded a mixture of at least four products.[18] Apparently,

(9) DeSilva, S. O.; Reed, J. N.; Snieckus, V. *Tetrahedron Lett.* **1978**, 5099. (b) Beak. P.; Brown, R. A. *J. Org. Chem.* **1979**, *44*, 4463. (c) Plauman, H. P.; Keay, B. A.; Rodrigo, R. *Tetrahedron Lett.* **1979**, 4921. (d) Zielger, F. E.; Fowler, K. W. *J. Org. Chem.* **1976**, *41*, 1564. (e) Commins, D. L.; Brown, J. D.; Mantlo, N. B. *Tetrahedron Lett.* **1982**, *23*, 3979. (f) Sinhababu, A. K.; Borchardt, R. T. *J. Org. Chem.* **1983**, *48*, 2356. (g) Prabhu, U.; Eapen, K. C.; Tamborski, C. *Ibid.* **1984**, *49*, 2792.

(10) Ladd, D. L.; Weinstock, J. *J. Org. Chem.* **1981**, *46*, 203 and references cited therein.

(11) The acetal **9** was previously reported not to undergo metalation with *n*-butyllithium and to afford a complex mixture of products from metalation with *tert*-butyllithium, followed by reaction with methyl iodide.[9c]

(12) Alder, K.; Rickert, H. F. *Ann.* **1936**, *524*, 180. For a brief discussion, see also: "The Merck Index", 9th ed.; Merck and Co., Inc.: Rahway, NJ, 1976; Vol. 9, p ONR-2.

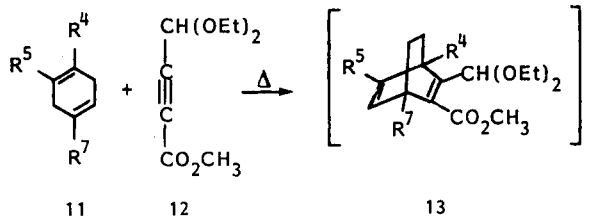
(13) Harland, P. A.; Hodge, P. *Synthesis* **1982**, 223; **1983**, 419. We regret having not referenced these key papers in our preliminary note on the Diels–Alder chemistry reported herein and wish to thank Professor Hodge for informing us of his work.

(14) The 1,3-dipolar cycloadditions of **12** have been studied. (a) Farina, F.; Martin, M. V.; Sanchez, F. *An. Quim.* **1982**, *78C*, 332. (b) Farina, F.; Fernadez, P.; Martin, M. R.; Martin, M. V.; Sanchez, F. *Ibid.* **1983**, *79C*, 333. (c) See also: Gorgues, A.; Simon, A.; LeCoq, A.; Corre, F. *Tetrahedron Lett.* **1981**, *22*, 625. (d) Professor F. Farina has informed us that he has studied the Diels–Alder reaction of **12** with simple dienes.

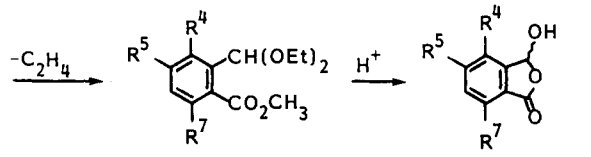
(15) Johnson, O. H.; Holum, J. R. *J. Org. Chem.* **1958**, *23*, 738.

(16) The conversion of 1-methoxycyclohexa-1,4-dienes to the conjugated isomer under Diels–Alder conditions has been studied and proposed to occur via a charge-transfer complex. Birch, A. J.; Dastur, K. P. *Tetrahedron Lett.* **1972**, 4195; *J. Chem. Soc., Perkin Trans. 1* **1973**, 1650.

(17) Alfaro, I.; Ashton, W.; McManus, L. D.; Newstead, R. C.; Rabone, K. L.: Rodgers, N. A.; Kernick, W. *Tetrahedron* **1970**, *26*, 201 and references cited therein.



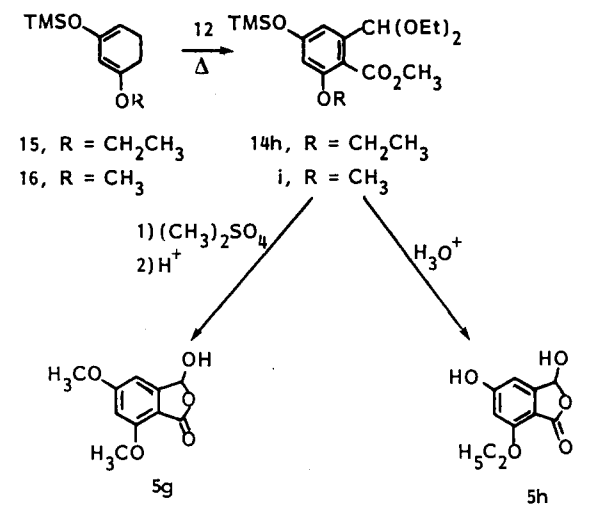
11 12 13



14 5

	R^4	R^5	R^7
d	H	H	OCH_3
e	H	H	O-n-Bu
f	OCH_3	H	OCH_3
g	H	OCH_3	OCH_3
h	H	OH	OEt

either the 1,4-cyclohexadiene to 1,3-cyclohexadiene isomerization was not clean or the Diels–Alder reaction was complicated. However, the 5,7-dioxygenation pattern in hydroxyphthalides can be obtained by reaction of **12** with dienes **15** or **16**. The use of **15** or **16** in the Diels–Alder reaction had the added advantage of the oxygen linkages in the ring being differentiated chemically, a feature of interest for the synthesis of compounds having different oxygen substituents. Compound **14h** was converted to **5h**

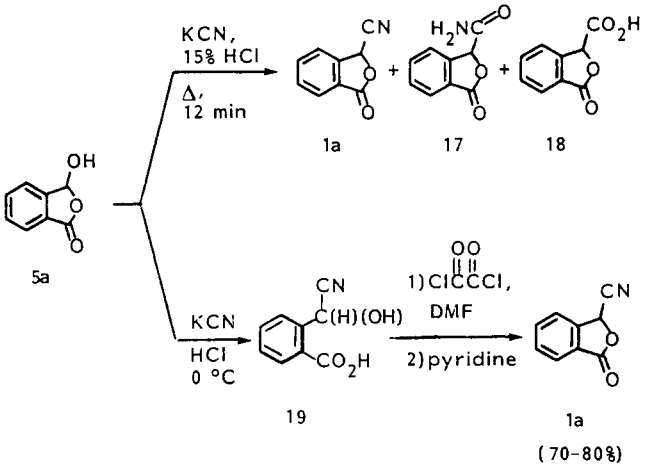


15, R = CH_2CH_3 14h, R = CH_2CH_3
16, R = CH_3 i, R = CH_3

5g 5h

by acid hydrolysis, while **14i** was reacted with dimethyl sulfate prior to hydrolysis to give the known **5g**[7a] (70% overall). Thus, the Diels–Alder reaction of **12** with 1,3-cyclohexadienes forms the basis of a short, high-yield route to a number of hydroxyphthalides.

3-Cyano-1(3*H*)-isobenzofuranones. An essential feature of the use of the 3-cyano-1(3*H*)-isobenzofuranones as annelating reagents in organic synthesis was their preparation in reasonable yield from hydroxyphthalides. Three different methods have been reported for the preparation of **1a**;[2a,d] however, yields and experimental procedures were not published.[19] The conditions of Robinson[20] for conversion of opianic acid to the corresponding 3-cyano-1(3*H*)-isobenzofuranone when applied to the commercially available **5a** gave a difficult-to-separate mixture of **1a**, **17**, and **18** in proportions that varied



5a 1a 17 18 19 1a (70–80%)

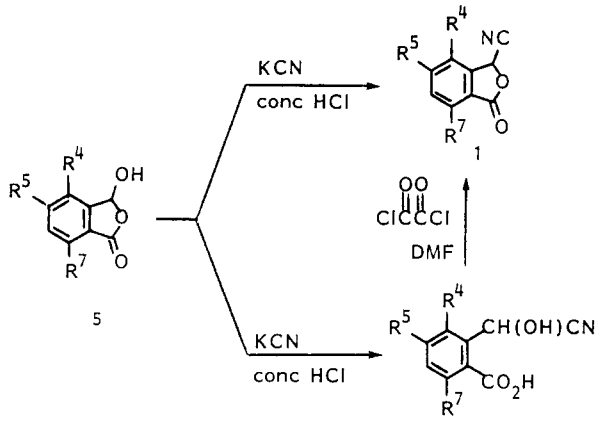
with the reaction conditions. While the use of longer reaction times and concentrated hydrochloric acid did afford good yields of **18**, **1** could not be obtained as the major product from the reaction despite extensive experimentation. Conversion of the acid **18** to the nitrile **1a** by reaction with chlorosulfonyl isocyanate[2a,20b] was explored, but, again, low yields of **1a** were obtained.

Finally, it was observed that if a 0 °C solution of **5a** and aqueous potassium cyanide was acidified with concentrated hydrochloric acid, a 77% yield of the cyanohydrin **19a** could be obtained by filtration. The structural assignment for this product rests with the ^1H NMR, ^{13}C NMR, and IR spectra because the material decomposes on standing. Initially, there was doubt as to the structure since attempts to cyclize the compound to **1a** with conventional reagents such as thionyl chloride, acetic anhydride, or *p*-toluenesulfonic acid in benzene at reflux gave mixtures of products that were not characterized. Surprisingly, addition of the crude cyanohydrin to the Vilsmeier salt prepared from dimethylformamide and oxalyl chloride followed by the addition of pyridine gave **1a** in 70–80% yield.

Having developed the conditions for conversion of **5a** to the corresponding 3-cyano-1(3*H*)-isobenzofuranone in the parent system, no difficulty was expected in performing this same conversion in the substituted systems. However, conversion of the substituted hydroxyphthalides to the corresponding 3-cyano-1(3*H*)-isobenzofuranones was dependent on the compound, and no general procedure was found. Thus, compounds **5d,f,g** under conditions for cyanohydrin formation gave **1d,f,g** directly. The hydroxyphthalides **5a–c,e** gave primarily the cyanohydrins which were then cyclized using the Vilsmeier salt to give the corresponding 3-cyano-1(3*H*)-isobenzofuranones. The reason for the uniqueness of the Vilsmeier salt in effecting the high-yield cyclization is unknown; however, the method may be of value in effecting other dehydrative cyclizations.

Summary. Methods have been developed for the preparation of a number of substituted derivatives of 3-cyano-1(3*H*)-isobenzofuranones. The compounds are now available as useful 1,4-dipole synthons in annelation chemistry. A future publication will present the utility of these compounds in the synthesis of daunomycinone analogues and other anthracyclinone systems.

(18) See also ref 13.
(19) Professor Kraus has informed us that the experimental data for the latest procedure was inadvertantly left out in a revision of the paper.
(20) (a) Freundler, M. P. *Bull. Soc. Chim.* **1914**, *15*, 465. Perkin, W. H.; Ray, N.; Robinson, R. *J. Chem. Soc.* **1925**, *127*, 740. (b) The Kraus group[2d] has recently reported this method to be unreliable.



	R^4	R^5	R^7
a	H	H	H
b	OCH_3	H	H
c	H	H	F
d	H	H	OCH_3
e	H	H	O-n-Bu
f	OCH_3	H	OCH_3
g	H	OCH_3	OCH_3

Experimental Section[21]

3-Hydroxy-4-methoxy-1(3*H*)-isobenzofuranone (5b). To a vigorously stirred −78 °C mixture of *N,N*-diethyl-3-methoxybenzamide (20.0 g, 96.6 mmol), tetramethylethylenediamine (16 mL, 106 mmol), and THF (150 mL) was added *sec*-butyllithium (85 mL of a 1.25 M solution) dropwise over 45 min. After stirring the cloudy yellow solution for 45 min, dry DMF (25 mL, 318 mmol) was added, and the solution was stirred for 30 min at −78 °C and then stirred for 15 h at room temperature. Water (100 mL) was added, and the solution was acidified to pH 1 with concentrated HCl. Workup afforded the crude *N,N*-diethyl-2-formyl-3-methoxybenzamide, which was dissolved in a mixture of HOAc (200 mL) and 10% HCl (200 mL). This solution was heated to reflux for 18 h and concentrated in vacuo at 40–45 °C, and the solid residue was dissolved in EtOAc (250 mL). The organic phase was extracted with saturated $NaHCO_3$ (3 × 100 mL), and the combined basic phase was acidified. The resulting solid was filtered, dried, and recrystallized from water to afford the product as colorless crystals (9.2 g, 52% overall), mp 155–156 °C (lit.[22] mp 157 °C).

***m*-Fluorobenzaldehyde Dimethyl Acetal (8).** A mixture of *m*-fluorobenzaldehyde (5.0 g, 40.3 mmol), trimethyl orthoformate (5 mL), methanol (25 mL), and *p*-toluenesulfonic acid (0.05 g) was stirred at room temperature for 1 h. The reaction mixture was quenched with 1% CH_3OH/KOH (10 mL), concentrated in vacuo, and then worked up as usual to afford after distillation the dimethyl acetal (5.3 g, 80%): bp 79 °C (0.8 torr); IR (neat) 1590 (m), 1490 (m), 1450 (m), 1440 (sh), 1355 (br m), 1270 (m), 1250 (m), 1190 (m), 1140 (m), 1100 (s), 1065 (s), 1055 (s), 870 (m), 780 (s) cm^{-1}: ^1H NMR δ 7.4–6.2 (m, 4 H), 5.38 (s, 1 H), 3.33 (s, 6 H); mass spectrum, exact mass calcd for $C_9H_{11}O_2F$ *m/e* 170.0743, obsd 170.0753.

3-Hydroxy-7-fluoro-1(3*H*)-isobenzofuranone (5c). To a −70 °C solution of the dimethyl acetal from above (5.3 g, 31 mmol) in THF (35 mL) was added dropwise *sec*-butyllithium (22.2 mL of a 1.4 M solution in hexane), and the red solution was stirred for 0.5 h. The solution was saturated with CO_2 for 5 min with the red color dissipating to yield a light yellow solution. After 10 min the reaction mixture was allowed to warm to room temperature, and after 30 min HCl (3.5 mL) was added. After concentration the solution was made basic with 5% KOH (25 mL), the neutral material extracted with Et_2O (2 × 40 mL), the base layer acidifed to pH 1 with HCl, and the product extracted with EtOAc (2 × 75 mL). Workup as usual afforded 4.5 g (86%) of the title compound, mp 111–119 °C, suitable for use in the next step. Recrystallization of this material from EtOAc/PE gave analytically pure material: mp 126–127 °C; IR 3400 (br s), 1740–1760 (structured s), 1630 (m), 1485 (m), 1300 (m), 1085 (s), 910 (m), 760 (m) cm^{-1}; ^1H NMR δ 7.8–7.1 (highly structured m, 3 H), 6.60 (br s, 1 H); mass spectrum, exact mass calcd for $C_8H_5O_3F$ *m/e* 168.0227, obsd 168.0226.

2,5-Dimethoxy-4-formylbenzoic Acid (10). To a −78 °C solution of 2,5-dimethoxybenzaldehyde dimethyl acetal (2.35 g, 11.1 mmol) and tetramethylenediamine (2.3 mL) in THF (50 mL) was added dropwise *sec*-butyllithium (11.9 mL of a 1.3 M solution in hexane), and the red-brown solution was stirred for 0.5 h. The solution was saturated with CO_2 for 5 min with the red color dissipating to yield a light yellow solution. The reaction was quenched with water (25 mL) and the neutral material extracted with Et_2O (2 × 30 mL). Acidification with concentrated HCl, cooling of the mixture, and filtration gave after drying 1.45 g (62%) of the title compound, mp 195–197 °C. Recrystallization (EtOAc) gave the analytical sample: mp 196–197 °C; IR 1740 (s), 1680 (s), 1410 (s), 1210 (s), 1020 (s) cm^{-1}; ^1H NMR δ 10.11 (s, 1 H), 7.82 (s, 1 H), 7.49 (s), 4.07 (s, 3 H), 3.96 (s, 3 H); mass spectrum, Exact mass calcd for $C_{10}H_{10}O_5$ *m/e* 210.0500, obsd 210.0514.

Methyl 4,4-Diethoxybutynoate (12). To a 0 °C solution of 3,3-diethoxy-1-propyne[15] (10 g, 78 mmol) and THF (30 mL) was added dropwise CH_3Li (53.7 mL of a 1.6 M solution, 86 mmol). This solution was then added to a −78 °C solution of methyl chloroformate (6.7 mL, 87 mmol) in THF (30 mL). The resulting light amber solution was allowed to warm to room temperature overnight and the reaction mixture was then quenched with water (100 mL). Workup as usual gave an amber oil which was distilled through a short-path head to yield a clear colorless liquid (12 g, 82%): bp 63–66 °C (0.15 mm); IR (neat) 2240 (m), 1740 (s), 1435 (s), 1250 (s, br), 1120 (s), 1050 (s), 1018 (s), 750 (s) cm^{-1}. ^1H NMR δ 5.3 (s, 1 H), 3.68 (s, 3 H), 3.3–3.8 (str m, 4 H), 1.13 (t, *J* = 9 Hz, 3 H). Anal. Calcd for $C_9H_{14}O_4$: C, 58.1; H, 7.5. Found: C, 57.7; H, 7.6.

Methyl 2-Formyl-6-methoxybenzoate Diethyl Acetal (14d). A mixture of methyl 4,4-diethoxybutynoate (4.0 g, 21.5 mmol) and 1-methoxy-1,4-cyclohexadiene (2.95 g, 26.8 mmol, 1.25 equiv) in dry toluene (1.5 mL) was heated (bath temperature 165 °C) for 6 h, after which time VPC analysis (5 ft × $^1/_8$ in. column of 5% OV-101 on 80–100 mesh Chromasorb G at 200 °C) showed disappearance of starting acetylene. The reaction mixture was distilled through a short-path head to yield a light yellow oil (4.55 g, 80%): bp 112–115 °C (0.07 mm); IR (neat) 1735 (s), 1590 (m), 1470 (s), 1270 (s), 1115 (s), 1070–1050 (s, br) cm^{-1}; ^1H NMR δ 7.4–7.2 (m, 2 H), 6.95–6.8 (m, 1 H), 5.65 (s, 1 H), 3.85 (s, 3 H), 3.76 (s, 3 H), 3.54 (q, *J* = 8 Hz, 4 H), 1.25 (t, *J* = 8 Hz, 3 H); ^{13}C NMR δ 168.1, 156.5, 137.9, 130.1, 122.3, 118.8, 111.1, 98.9, 61.0 (2 C), 55.9, 51.9, 14.8 (2 C); mass spectrum, exact mass calcd for $C_{14}H_2{}^0O_5$ *m/e* 268.1311, obsd 268.1283.

Methyl 2-Formyl-6-*n*-butoxybenzoate Diethyl Acetal (14e). In a manner similar to the above, **12** (4.0 g, 21.5 mmol)

(21) The following abbreviations have been used throughout the Experimental Section: *n*-butyllithium (*n*-BuLi), *sec*-butyllithium (sec-BuLi), chloroform ($CHCl_3$), cyclohexane (C_6H_{12}), dimethylformamide (DMF), dimethyl sulfoxide (Me_2SO), ethanol (EtOH), ether (Et_2O), hydrochloric acid (HCl), hexane (H), lithium diisopropylamide (LDA), methanol (CH_3OH), methylene chloride (CH_2Cl_2), petroleum ether (PE), tetrahydrofuran (THF). All melting points below 220 °C were taken with a Thomas-Hoover capillary melting-point apparatus and are uncorrected. Measurements with standard samples indicate that the reported melting points are probably 1–2 °C lower than the correct value. Infrared spectra were taken on a Perkin-Elmer Model 283B grating spectrometer. ^1H NMR spectra were recorded at 80 MHz in $CDCl_3$ on an IBM NR-80 unless otherwise noted. Apparent multiplicities are reported, and in some cases, signals reported as triplets are in fact closely spaced doublets of doublets. ^{13}C NMR spectra (tetramethylsilane reference) were recorded on an IBM NR-80 instrument at 20 MHz in $CDCl_3$ unless otherwise noted. Mass spectra and exact mass measurements were obtained by C. R. Weisenberger on a Kratos MS-30 mass spectrometer connected to a DS-55 data system. Tetrahydrofuran was freshly distilled from benzophenone/sodium prior to use. All other solvents used for reactions were freshly dried and distilled. All reactions were run under nitrogen or argon atmosphere. Analytical samples were analyzed by Scandinavian Microanalytical Laboratory. Aluminum oxide and silica gel were from E. Merck Co. "Workup as usual" consisted of extraction of the product (CH_2Cl_2 or Et_2O), drying over calcium sulfate or sodium sulfate, and concentration in vacuo followed by drying under vacuum.

(22) Marumo, S.; Sasaki, K.; Ohkuma, K.; Ansai, K.; Suzuki, S. *Agric. Biol. Chem.* **1968**, 209.

and 1-*n*-butoxy-1,4-cyclohexadiene (3.25 g, 21.5 mmol) in dry toluene (2 mL) were heated at 170 °C for 5 h, after which time additional diene (1.5 g) was added. After 20 h of reaction time, distillation through a short-path head gave **14e** as a light yellow oil (5.4 g, 81%): bp 125–130 °C (0.07 mm): IR (neat) 2960 (br s), 1730 (s), 1590 (s), 1460 (s), 1265 (s, br), 1110 (s), 1060 (s, br) cm^{-1}; ^1H NMR δ 7.41–7.12 (m, 2 H), 6.83 (dd, J = 9, 2.4 Hz, 1 H), 5.65 (s, 1 H), 3.97 (t, J = 7 Hz, 2 H), 3.88 (s, 3 H), 3.53 (center of overlapping q, J = 9 Hz, 4 H), 1.82–1.38 (m, 4 H), 1.21 (t, J = 9 Hz, 3 H), 0.94 (t, J = 7 Hz, 3 H); ^{13}C NMR δ 168.2, 156.1, 137.9, 130.0, 122.8, 118.7, 112.3, 99.1, 68.5, 61.1 (2 C), 51.7, 31.1, 19.0, 14.9 (2 C), 13.7; mass spectrum, exact mass calcd for $C_{17}H_{26}O_5$ m/e 310.1780, obsd 310.1817.

Methyl 2-Formyl-3,6-dimethoxybenzoate Diethyl Acetal (14f). In a manner similar to the above, **12** (3.8 g, 20.4 mmol) and 1,4-dimethoxy-1,4-cyclohexadiene (4.57 g, 32.6 mmol, 1.6 equiv) in dry toluene (2.0 mL) were heated (bath temperature 170 °C) for 18 h. Additional diene [1.5 g (6.1 g total), 2.1 equiv] in toluene (2 mL) was added, and heating was continued for an additional 30 h, after which time VPC indicated no starting **12**. Distillation via a short-path head yielded **14f** as a light yellow oil (4.85 g, 80%): bp 126–130 °C (10^{-4} mm); IR (neat) 1740 (s), 1600 (m), 1460 (s, br), 1300–1000 (s, br), 800 (m), 720 (s) cm^{-1}; ^1H NMR δ 6.74 (s, 2 H), 5.65 (s, 1 H), 3.2–3.8 (overlapping, 13 H), 1.07 (t, J = 7.5 Hz, 3 H); ^{13}C NMR δ 168.0, 151.5, 150.5, 126.0, 123.9, 112.8, 112.1, 97.5, 62.3 (2 C), 56.6 (2 C), 51.8, 14.9 (2 C); mass spectrum, exact mass calcd for $C_{15}H_{22}O_6$ m/e 298.1516, obsd 298.1420.

Methyl 2-Formyl-4-(trimethylsiloxy)-6-ethoxybenzoate Diethyl Acetal (14h). The silyl enol ether[23] (4.5 g, 14.9 mmol, ca. 70:30 mixture with the ketone prepared as below) and **12** (2.7 g, 14.3 mmol) in toluene (2 mL) were heated at a bath temperature of 150 °C for 16 h and then distilled to afford 4.85 g (90%) of a light tan oil: bp 138–142 °C (5 × 51.6, IR (neat) 2980 (m), 1730 (s), 1600 (s), 1260 (s), 1170 (s), 1060 (s), 860 (br, s) cm^{-1}; ^1H NMR δ 6.68 (d, J = 2.2 Hz, 1 H), 6.33 (d, J = 2.2 Hz, 1 H), 5.60 (s, 1 H), 3.95 (q, J = 7 Hz, 2 H), 3.85 (s, 3 H), 3.53 (overlapping q, J = 7 Hz, 4 H), 1.33 (t, J = 7 Hz, 3 H), 1.18 (t, J = 7 Hz, 6 H), 0.24 (s, 9 H); ^{13}C NMR δ 168.2, 157.4, 156.9, 139.3, 116.2, 110.1, 104.6, 98.8, 64.3, 61.1 (2 C), 51.6, 14.8 (2 C), 14.4, –0.03 (3 C); mass spectrum, exact mass calcd for $C_{18}H_{30}O_6Si$ m/e 370.1820, obsd 370.1816.

Methyl 2-Formyl-4-(trimethylsiloxy)-6-methoxybenzoate Diethyl Acetal (14i). To a –78 °C solution of diisopropylamine (3.17 g, 31.4 mmol) in THF (25 mL) was added *n*-butyllithium (19.8 mL of a 1.6 M solution in hexane). To this mixture was added dropwise 3-methoxycyclohexenone[23] (4.0 g, 28.6 mmol) in THF (15 mL), and the reaction mixture was stirred for 10 min, followed by addition of trimethylsilyl chloride (3.85 g, 35.6 mmol). After stirring for 1 h at –78 °C, the solution was poured into cold 5% $NaHCO_3$ and worked up as usual. Distillation through a short-path head gave 3.7 g of a colorless liquid, bp 58–60 °C (0.15 mm), whose ^1H NMR spectrum indicated a 3:1 mixture of silyl ether and starting material. This above material, **12** (1.9 g, 10.1 mmol), and dry toluene (2 mL) were heated at 160 °C for 20 h. Distillation through a short-path head gave the title compound as a light golden oil (3.2 g, 91%): bp 125–130 °C (0.001 mm); IR (neat) 1730 (s), 1600 (s), 1340 (s), 1260 (s, br), 1160 (s), 1070 (s, br), 1055 (s), 860 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 6.7 (d, J = 2 Hz, 1 H), 6.33 (d, J = 2 Hz, 1 H), 5.6 (s, 1 H), 3.85 (s, 3 H), 3.75 (s, 3 H), 3.3–3.8 (overlapping q, J = 8 Hz, 4 H), 1.2 (t, J = 8 Hz, 6 H), 0.3 (s, 9 H); ^{13}C NMR δ 168.0, 157.9, 156.9, 139.3, 115.2, 110.0, 103.5, 98.7, 62.2, (2 C), 55.7, 51.7, 14.8 (2 C), 0.0 (3 C); mass spectrum, exact mass calcd for $C_{17}H_{28}O_6Si$ m/e 356.1655, obsd 356.1675.

3-Hydroxy-7-methoxy-1(3*H*)-isobenzofuranone (5d). A mixture of **14d** (4.5 g, 16.7 mmol) in glacial HOAc (15 mL) and 10% aqueous HCl (15 mL) was heated to reflux for 12 h. The reaction mixture was concentrated in vacuo to a solid residue which was extracted with ethyl acetate (8 × 10 mL). Workup yielded a sweet-smelling off-white solid (2.35 g, 79%), mp 142–144 °C. Recrystallization from hot water yielded white needles (2.05 g, 69%), mp 151–153 °C (lit.[4d] mp 152–154 °C), showing an IR spectrum identical with that of an authentic sample.

3-Hydroxy-7-*n*-butoxy-1(3*H*)-isobenzofuranone (5e). A mixture of **14e** (0.89 g, 2.87 mmol) in glacial HOAc (5 mL) and 5% aqueous HCl (5 mL) was heated to 70 °C for 4 h, then concentrated in vacuo, and extracted with EtOAc (5 × 20 mL). Concentration and crystallization of the crude solid from EtOAc/H gave 0.46 g (72%) of a white solid: mp 96–98 °C. The analytically pure material showed the following: mp 99–100 °C; IR 3400 (m), 1740 (s), 1620 (m), 1490 (m), 1325 (m), 1290 (m), 1040 (m), 925 (m) cm^{-1}; ^1H NMR δ 7.58 (t, J = 9 Hz, 1 H), 7.0 (d, J = 9 Hz, 1 H), 6.8 (d, J = 9 Hz, 1 H), 6.47 (d, J = 7 Hz, 2 H), 4.1 (t, J = 6 Hz, 2 H), 3.78 (d, J = 7 Hz, 1 H), 1.9–1.4 (m, 4 H), 0.93 (t, J = 6 Hz, 3 H); ^{13}C NMR δ 167.7, 157.6, 149.2, 136.7, 114.9, 113.8, 113.4, 96.6, 68.8, 30.6, 18.9, 13.6; mass spectrum, exact mass calcd for $C_{12}H_{14}O_4$ m/e 222.0892, obsd 222.0906.

3-Hydroxy-4,7-dimethoxy-1(3*H*)-isobenzofuranone (5f). A solution of ester acetal **14f** (3.0 g) and Et_2O (125 mL) was vigorously stirred with 5% aqueous HCl (65 mL) for 5 min. Sodium chloride (4 g) was then added, the organic phase was separated, the aqueous phase was back extracted with Et_2O (20 mL), and the combined ethereal layers were worked up as usual to yield a crude yellow solid, which was triturated with cold CH_3OH (10 mL) and filtered to yield white crystals (1.9 g, 85%) of methyl 2-formyl-3,6-dimethoxybenzoate: mp 104–105 °C; IR 1735 (s), 1685 (s), 1495 (s), 1440 (m), 1280 (s), 1060 (s), 955 (m), 820 (m), 715 (m) cm^{-1}; ^1H NMR δ 10.37 (s, 1 H), 7.05 (center of AB, J = 9.2 Hz, $\Delta\nu$ = 16.2 Hz, 2 H), 3.92 (s, 3 H), 3.82 (s, 3 H), 3.78 (s, 3 H); ^{13}C NMR δ 188.6, 167.5, 156.0, 150.2, 123.8, 122.3, 119.1, 113.6, 56.9, 56.3, 52.6; mass spectrum, exact mass calcd for $C_{11}H_{12}O_5$ m/e 224.068 47, obsd 224.0715.

To the above aldehyde/ester (1.9 g), CH_3OH (25 mL), and ice (15 g) was added 20% aqueous KOH (15 mL). The resulting yellow solution was stirred for 24 h at room temperature, cooled to 0 °C, acidified with cold HCl (7 mL), and then concentrated to half of the original volume. The resulting slurry was extracted with ethyl acetate (3 × 35 mL), dried, and concentrated in vacuo to yield a light tan product (1.44 g, 68%), mp 188–190 °C. The analytical sample showed the following: mp 192–194 °C; IR 3400 (m, br), 1750 (s, br), 1505 (s), 1395 (s), 1370 (s), 1060 (s), 1040 (s) cm^{-1}; ^1H NMR δ 7.01 (center of AB, J_{AB} = 10.5 Hz, $\Delta\nu$ = 17.4 Hz, 2 H), 6.55 (br s, 1 H), 3.87 (s, 3 H), 3.83 (s, 3 H); mass spectrum, exact mass calcd for $C_{10}H_{10}O_5$ m/e 210.052 82, obsd 210.0558.

3-Hydroxy-5,7-dimethoxy-1(3*H*)-isobenzofuranone (5g). A mixture of **14i** (2 g, 5.62 mmol), K_2CO_3 (5 g, 35 mmol), and $(CH_3)_2SO_4$ (5.3 g, 42 mmol) in $(CH_3)_2CO$ (80 mL) was heated to reflux overnight and then filtered and concentrated in vacuo to give a light orange oil. The intermediate dimethoxy ester acetal was dissolved in glacial HOAc (20 mL), 5% HCl (20 mL) was added, and the solution was heated at 65 °C for 5 h, then poured into water (20 mL), and extracted with EtOAc (4 × 30 mL). Workup and trituration with cold ethyl acetate gave a white solid (715 mg, 64%), mp 185–186.5 °C (lit.[7a] mp 186–189 °C).

3,5-Dihydroxy-7-ethoxy-1(3*H*)-isobenzofuranone (5h). A solution of **14h** (1.0 g, 2.7 mmol), HOAc (15 mL), and 5% HCl (15 mL) was heated to 90 °C for 5 h. Concentration in vacuo gave a tan solid, which was extracted with hot EtOAc (6 × 10 mL). The combined EtOAc portions were worked up to yield 0.47 g (85 %) of **5h**, mp 215–217 °C. Recrystallization (CH_3OH) gave the analytical sample: mp 220–221 °C; IR 3440 (m), 3225 (m, br), 1745 (s), 1720 (s), 1610 (s), 1350 (s), 1230 (s), 1220 (s), 1170 (s) cm^{-1}; ^1H NMR δ 6.58 (m, 2 H), 6.39 (br s, 1 H), 5.60 (s, 1 H), 4.15 (q, J = 7 Hz, 2 H), 1.40 (t, J = 7 Hz, 3 H); mass spectrum, exact mass calcd for $C_{10}H_{10}O_5$ m/e 210.0528, obsd 210.0513.

3-Cyano-1(3*H*)-isobenzofuranone (1a). A mixture of potassium cyanide (42 g, 636 mmol), water (250 mL), and 3-hydroxy-1(3*H*)-isobenzofuranone (Aldrich Chemical Co., 20 g, 132.5 mmol) was stirred and cooled to 0 °C to effect a homogeneous clear yellow solution. Ice (~150 g) was then added, followed by addition of HCl (150 mL). The mixture was stored for 12 h at –15 °C, and the resulting white needles were filtered and vacuum dried to give the cyanohydrin (18.2 g, 77%) suitable for use in the next step: mp 65–67 °C; IR 3460 (s), 3400–2400 (br m), 2260 (w), 1680 (s), 1260 (s), 1050 (m), 740 (m); ^1H NMR δ (acetone-d_6, 90 MHz) 7.63–6.74 (m, 4 H), 5.58 (s, 1 H); ^{13}C NMR

(23) (a) Gannon, W.; House, H. O. *Org. Synth.* **1960**, *40*, 41. (b) No attempt was made to obtain the pure silyl enol ether since the Diels–Alder reaction and subsequent distillation gave a pure product in excellent overall yield.

δ (Me_2SO-d_6, 22.5 MHz) 167.6, 138.2, 132.7 130.7, 128.8, 128.2, 126.6, 120.2, 59.1.

A rapidly stirred mixture of oxalyl chloride (15 mL, 172 mmol, 1.7 equiv) and dry acetonitrile (120 mL) was cooled to −12 °C (dry ice/ethylene glycol), and then dry DMF (15 mL, 193.2 mmol, 1.9 equiv) was added. Vigorous gas evolution occurred, and a white solid precipitated. To this mixture was added the cyanohydrin (18.2 g, 102 mmol) in acetonitrile (100 mL). The solution became clear yellow and was stirred for 5 min, followed by addition of pyridine (28 mL, 346 mmol, 3.4 equiv). The resulting dark yellow solution was stirred for 30 min at −15 °C, then poured into cold aqueous 5% HCl (300 mL), and extracted with Et_2O (3 × 175 mL). The combined organics were washed with saturated sodium bicarbonate (150 mL) and worked up as usual to afford a dark yellow solid. Filtration of this material through silica gel (10 × 1 in. column, CH_2Cl_2 as eluant) gave light yellow crystals (13.2 g, 82%), mp 116–118 °C. A sample recrystallized from EtOAc/H gave the pure compound as white crystals: mp 120–121 °C; IR 1780 (s), 1600 (m), 1465 (s), 1270 (s), 1100 (s), 1040 (s), 1020 (s), 740 (s) cm^{-1}; ^1H NMR δ ($CDCl_3$, 90 MHz) 8.1–7.6 (m, 4 H), 6.2 (s, 1 H); ^{13}C NMR δ ($CDCl_3$, 22.5 MHz) 161.0, 141.8, 135.6, 131.3, 126.5, 124.3, 122.8, 113.9, 65.7; mass spectrum, exact mass calcd for $C_9H_5NO_2$ m/e 159.0320, obsd 159.0324.

3-Cyano-4-methoxy-1(3*H*)-isobenzofuranone (1b). A solution of KCN (300 mg, 4.5 mmol), water (10 mL), and **5b** (300 mg, 1.66 mmol) was cooled to 0 °C. After 7 min, ice (15 g) was added to the light yellow solution, followed by addition of HCl (5 mL). The white cyanohydrin immediately precipitated and was filtered and dried to yield a white powder (280 mg, 82%), which was used directly in the next step: mp 114–116 °C dec; IR 3500–2400 (br), 2245 (w), 1670 (s), 1585 (s), 1460 (s), 1440 (s), 1270 (s), 1050 (s), 750 (s) cm^{-1}; ^1H NMR δ ($CDCl_3$, 80 MHz) 7.7–7.17 (m, 3 H), 6.47 (s, 1 H), 3.96 (s, 3 H).

The Vilsmeier reagent was formed from acetonitrile (10 mL), oxalyl chloride (0.4 mL, 4.45 mmol, 3.3 equiv), and DMF (0.4 mL, 5.5 mmol) as for the parent system. To this mixture was added the cyanohydrin from above (280 mg, 1.35 mmol) in acetonitrile (8 mL), the solution was stirred for 1 min, then pyridine (0.8 mL, 10.35 mmol) was added, and the solution was stirred for 15 min at 0 °C. The reaction mixture was poured into 5% aqueous HCl (30 mL), and the product was extracted with ether (3 × 20 mL). The combined ethereal layers were washed with 5% $NaHCO_3$ (30 mL) and worked up as usual to yield a white crystalline solid (128 mg, 70%): mp 162–163 °C; IR 1780 (s), 1590 (s), 1390 (s), 1370 (s), 1090 (m), 1030 (s), 1015 (s), 740 (s) cm^{-1}; ^1H NMR δ 7.55–7.40 (m, 2 H), 7.15–7.10 (m, 1 H), 5.85 (s, 1 H), 3.88 (s, 3 H); ^{13}C NMR δ 167.6, 154.6, 133.4, 129.3, 126.1, 117.3, 116.5, 113.5, 64.1, 56.1; mass spectrum, exact mass calcd for $C_{10}H_7NO_3$ m/e 189.0426, obsd 189.0427.

3-Cyano-7-fluoro-1(3*H*)-isobenzofuranone (1c). A solution of KCN (2.1 g, 30.8 mmol), water (3.5 mL), and **5c** (0.71 g, 4.2 mmol) was cooled to 0 °C. Concentrated HCl (14 mL) was added, and the solution was stirred for 10 min and then extracted with EtOAc (3 × 50 mL). Workup as usual gave a yellow-orange oil, which was dried under vacuum, dissolved in CH_3CN (8 mL), and added to the Vilsmeier salt prepared from oxalyl chloride (1.3 g) and DMF (1.23 mL) in the usual manner. After stirring for 1 min at 0 °C, pyridine (1.7 mL) was added, and the solution was stirred for an additional 15 min. Workup as for the parent system gave a dark red oil, which was recrystallized from CH_3OH to afford 0.425 g (57%) of the title compound in two crops, mp 117–120 °C. An additional crystallization (CH_3OH) gave the pure material: mp 121–123 °C; IR 1780 (s), 1630 (m), 1610 (m), 1490 (m), 1280 (m), 1260 (m), 1070 (m), 1025 (m), 995 (s), 800 (m) cm^{-1}; ^1H NMR δ 8.0–7.6 (str m, 1 H), 7.6–7.2 (str m, 2 H), 6.1 (s, 1 H); mass spectrum, exact mass calcd for $C_9H_4NO_2F$ m/e 177.0226, obsd 177.0233.

3-Cyano-7-methoxy-1(3*H*)-isobenzofuranone (1d). To a solution of KCN (7.5 g, 11.36 mmol) and water (35 mL) was added **5d** (3.0 g, 16.7 mmol). The resulting clear dark yellow solution was stirred for 10 min at room temperature and then cooled to 0 °C with an ice bath. After addition of ice, HCl (25 mL) was added, and the resulting clear colorless solution was removed from the ice bath and stored at room temperature for 5 h. Filtration and drying yielded white crystals (2.6 g, 83%): mp 154–156 °C (lit.[2b] 120–127 °C, lit.[2d] 147–148.5 °C); IR 1795 (s), 1620 (s), 1605 (s), 1500 (s), 1300 (s), 1200 (s), 1010 (s, br), 790 (s), 760 (m), 690 (m) cm^{-1}; ^1H NMR δ 7.78 (t, J = 10 Hz, 1 H), 7.21 (overlapping d, 2 H), 6.05 (s, 1 H), 4.05 (s, 3 H); ^{13}C NMR δ (Me_2SO-d_6, 22.5 MHz) 165.1, 158.2, 144.5, 138.0, 115.2, 114.5, 113.3, 110.6, 65.1, 56.0; mass spectrum, exact mass calcd for $C_{10}H_7NO_3$ m/e 189.0429, obsd 189.0427.

3-Cyano-7-*n*-butoxy-1(3*H*)-isobenzofuranone (1e). To a solution of KCN (3.5 g, 53 mmol) in water (30 mL) was added **5e** (900 mg, 4.05 mmol). After stirring for 15 min at room temperature, the clear solution was cooled in an ice bath and ice (45 g) was added, followed by addition of HCl (30 mL). The solution was stored for 12 h at room temperature, filtered, and air dried to yield white fibrous crystals (740 mg, 75%), which were used directly in the next step: mp 95–97 °C; IR 3650–2500 (br), 1710 (s), 1510 (m), 1285 (s), 1270 (s), 1045 (m), 765 (m) cm^{-1}; ^1H NMR δ 7.7 (t, J = 9 Hz, 1 H), 7.3–7.05 (m overlapping $CHCl_3$, 2 H), 5.96 (s, 1 H), 4.17 (t, J = 7 Hz, 2 H), 2.0–1.5 (m, 4 H), 1.0 (t, J = 7 Hz, 3 H); mass spectrum, exact mass calcd for $C_{13}H_{15}NO_4$ m/e 249.1001, obsd 249.1011.

A solution of the Vilsmeier reagent was prepared as described for the parent system from oxalyl chloride (0.38 mL, 4.37 mmol, 1.5 equiv), acetonitrile (10 mL), and DMF (0.4 mL, 5.17 mmol, 1.75 equiv), after which the product from above (725 mg, 2.9 mmol) in acetonitrile (15 mL) was added to the salt. The solution became clear yellow and was stirred for 1 min, and then pyridine (1 mL, 12.4 mmol, 4.3 equiv) was added. The solution was stirred for 10 min at 0 °C, then poured into 5% aqueous HCl (35 mL), and extracted with diethyl ether (2 × 35 mL). Workup afforded a yellow solid, which was filtered through silica gel (6 in. × 0.5 in. column, CH_2Cl_2 as eluant) to yield a white solid (635 mg, 95%): mp 88–88.5 °C; IR 1800 (s), 1620 (s), 1600 (s), 1490 (s), 1295 (s), 1285 (s), 1195 (s), 1035 (s), 1020 (s), 990 (s), 790 (s) cm^{-1}; ^1H NMR δ 7.75–7.14 (str m, 3 H), 5.89 (s, 1 H), 4.29 (t, J = 7 Hz, 2 H), 2.0–1.4 (m, 4 H), 1.04 (t, J = 7 Hz, 3 H); ^{13}C NMR δ 165.3, 158.8, 144.1, 137.7, 114.2, 113.9, 113.8, 112.2, 69.0, 64.6, 30.6, 18.9, 13.6; mass spectrum, exact mass calcd for $C_{13}H_{13}NO_3$ m/e 231.0895, obsd 231.0915.

3-Cyano-4,7-dimethoxy-1(3*H*)-isobenzofuranone (1f). A solution of KCN (2.8 g, 42.4 mmol), water (25 mL), and **5f** (700 mg, 3.3 mmol) was cooled to 0 °C. After addition of ice (30 g), cold HCl (25 mL) was added, and the solution was stored at room temperature overnight. The precipitated solid was filtered and dried to yield a light tan solid (675 mg, 92%): mp 151–153 °C; IR 1795 (s), 1780 (s), 1510 (s), 1280 (s), 1075 (s), 1025 (s), 1015 (s), 830 (s) cm^{-1}; ^1H NMR δ 7.1 (center of AB, J = 10 Hz, $\Delta\nu$ = 17.4 Hz, 2 H), 5.90 (s, 1 H), 3.9 (s, 3 H), 3.85 (s, 3 H); ^{13}C NMR δ 165.4, 152.5, 147.8, 130.6, 118.7, 114.6, 113.1, 108.5, 63.2, 56.5, 56.3; mass spectrum, exact mass calcd for $C_{11}H_9NO_4$ m/e 219.053 15, obsd 219.0515.

3-Cyano-5,7-dimethoxy-1(3*H*)-isobenzofuranone (1g). A solution of KCN (1.75 g, 25.7 mmol), water (8 mL), and **5g** (355 mg, 1.7 mmol) was cooled to 0 °C. Ice (10 g) was added, followed by addition of concentrated HCl (8 mL), and the solution was stored at room temperature for 4 h. Filtration and drying gave a white powder (300 mg). TLC (1% CH_3OH/CH_2Cl_2) showed two spots: the faster moving spot being product and the slower spot presumably being cyanohydrin. This crude product was chromatographed on silica gel (3 in. × 0.5 in. column, CH_2Cl_2 as eluant) to give a white foam, which was triturated with ether to give a white solid (263 mg, 72%): mp 134–135 °C; IR 1780 (s), 1610 (s), 1590 (s), 1335 (s), 1225 (s), 1210 (s), 1160 (s), 1015 (s), 1005 (s) cm^{-1}; ^1H NMR δ 6.65 (str m, 1 H), 6.53 (str m, 1 H), 5.89 (s, 1 H), 3.96 (s, 3 H), 3.92 (s, 3 H); ^{13}C NMR δ 168.0, 165.2, 160.1, 146.6, 114.2, 104.7, 110.8, 98.6, 64.6, 56.2 (2 C); mass spectrum, exact mass calcd for $C_{11}G_9NO_4$ m/e 219.0532, obsd 219.0532.

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