Synthesis D. Mal et al. Paper

Synthesis, Rearrangement, and Hauser Annulation of 3-Isocyanophthalides

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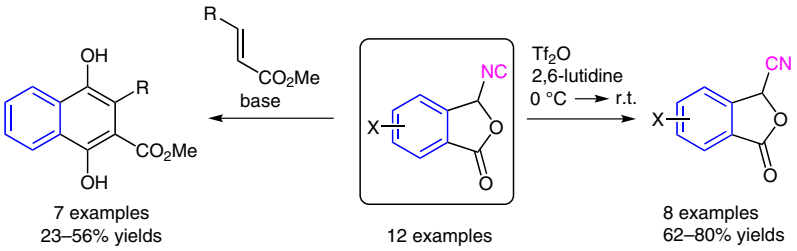

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Abstract 3-Isocyanoisobenzofuran-1(3*H*)-ones (phthalides) were prepared in two steps from the corresponding phthalaldehydic acids. The 3-isocyanoisobenzofuran-1(3*H*)-ones are readily rearranged to the corresponding 3-cyanoisobenzofuran-1(3*H*)-ones using triflic anhydride and 2,6-lutidine, thus enabling the synthesis of 3-cyanoisobenzofuran-1(3*H*)-ones without using toxic cyanide. Furthermore their annulation with Michael acceptors results in direct formation of 1,4-naphthoquinols/1,4-naphthoquinones in moderate yields.

Key words 3-isocyanoisobenzofuran-1(3*H*)-ones, synthesis, Hauser annulations, rearrangement, 3-cyanoisobenzofuran-1(3*H*)-ones

The Hauser annulation[1] is an established method for the regiospecific synthesis of 1,4-dihydroxynaphthalenes in a one-pot operation from 3-(phenylsulfonyl)isobenzofuran-1(3*H*)-ones and a Michael acceptor (Figure 1). It is viewed as a domino reaction sequence consisting of initial lateral deprotonation, Michael addition, followed by Dieckmann/Claisen cyclization and elimination of the phenylsulfinate ion. The annulation works well when 3-cyanoisobenzofuran-1(3*H*)-ones **1** are used in place of sulfonylisobenzofuran-1(3*H*)-ones (Figure 1).[2] The efficiency of annulation is significantly improved using lithium *tert*-butoxide or lithium hexamethyldisilazanide as the base.[3] In many instances, 3-cyanoisobenzofuran-1(3*H*)-ones **1** in conjunction with lithium *tert*-butoxide are the most effective combination for the annulation.[4]

However, all the syntheses of 3-cyanoisobenzofuran-1(3*H*)-ones **1** require toxic potassium cyanide or trimethylsilyl cyanide,[5] and the toxicity of the reagents remains a deterrent to their large-scale preparation. Consequently, our aim was to explore the chemistry of hitherto unknown 3-isocyanoisobenzofuran-1(3*H*)-ones **2**, since it is conceivable

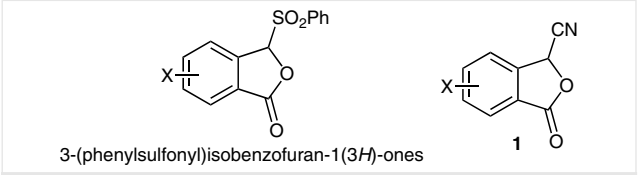
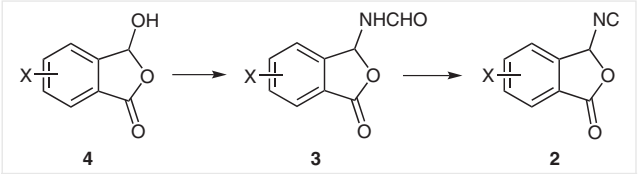


Figure 1 Established Hauser donors

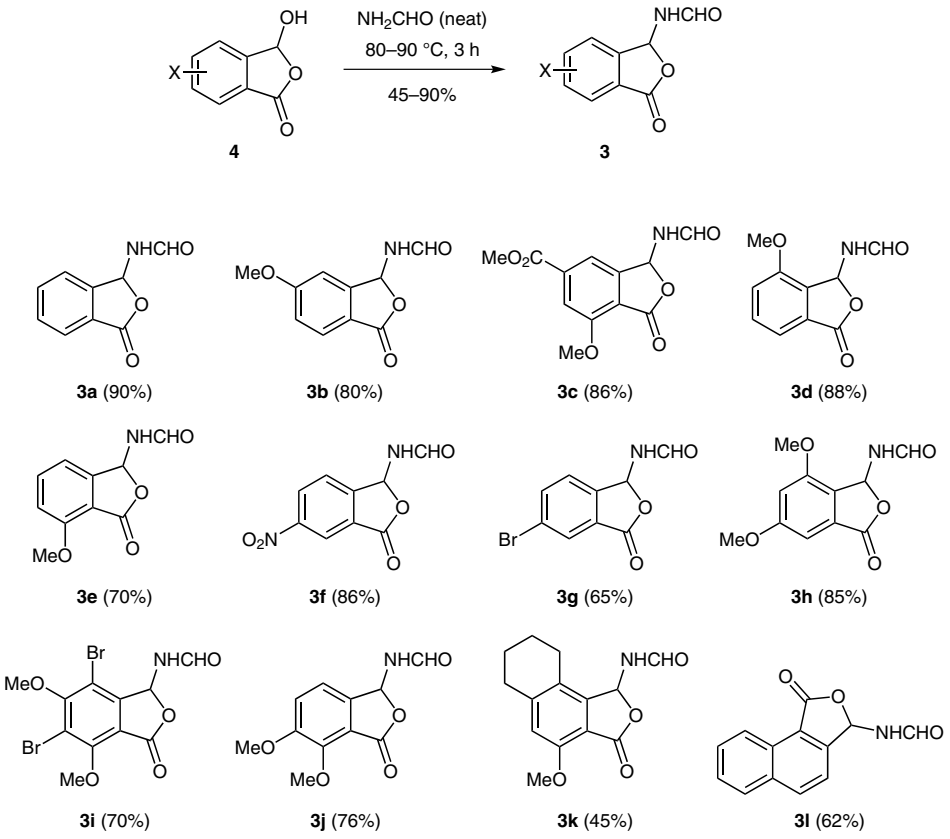
that they can be synthesized without the use of toxic cyanides. Furthermore, 3-isocyanoisobenzofuran-1(3*H*)-ones **2** can be rearranged to 3-cyanoisobenzofuran-1(3*H*)-ones **1**, as well as be used in multicomponent reactions.[6] Herein, we report the synthesis, rearrangement, and annulation reactivity of 3-isocyanoisobenzofuran-1(3*H*)-ones **2**.

For the synthesis of 3-isocyanoisobenzofuran-1(3*H*)-ones **2**, we considered the use of 3-(formylamino)isobenzofuran-1(3*H*)-ones **3** as precursors, since they were expected to be accessible from phthalaldehydic acids **4**[5c,7] (Scheme 1).



Scheme 1 Proposed route for the synthesis of 3-isocyanoisobenzofuran-1(3*H*)-ones

Initially, a solution of 2-formylbenzoic acid (phthalaldehydic acid, **4a**, X = H) in benzene was heated with formamide in the presence of 4-toluenesulfonic acid to give 3-(formylamino)isobenzofuran-1(3*H*)-one (**3a**, X = H); although the reaction was successful, the yield was ~25%. Further studies increased the yield of **3a** to 90% by simply heat-



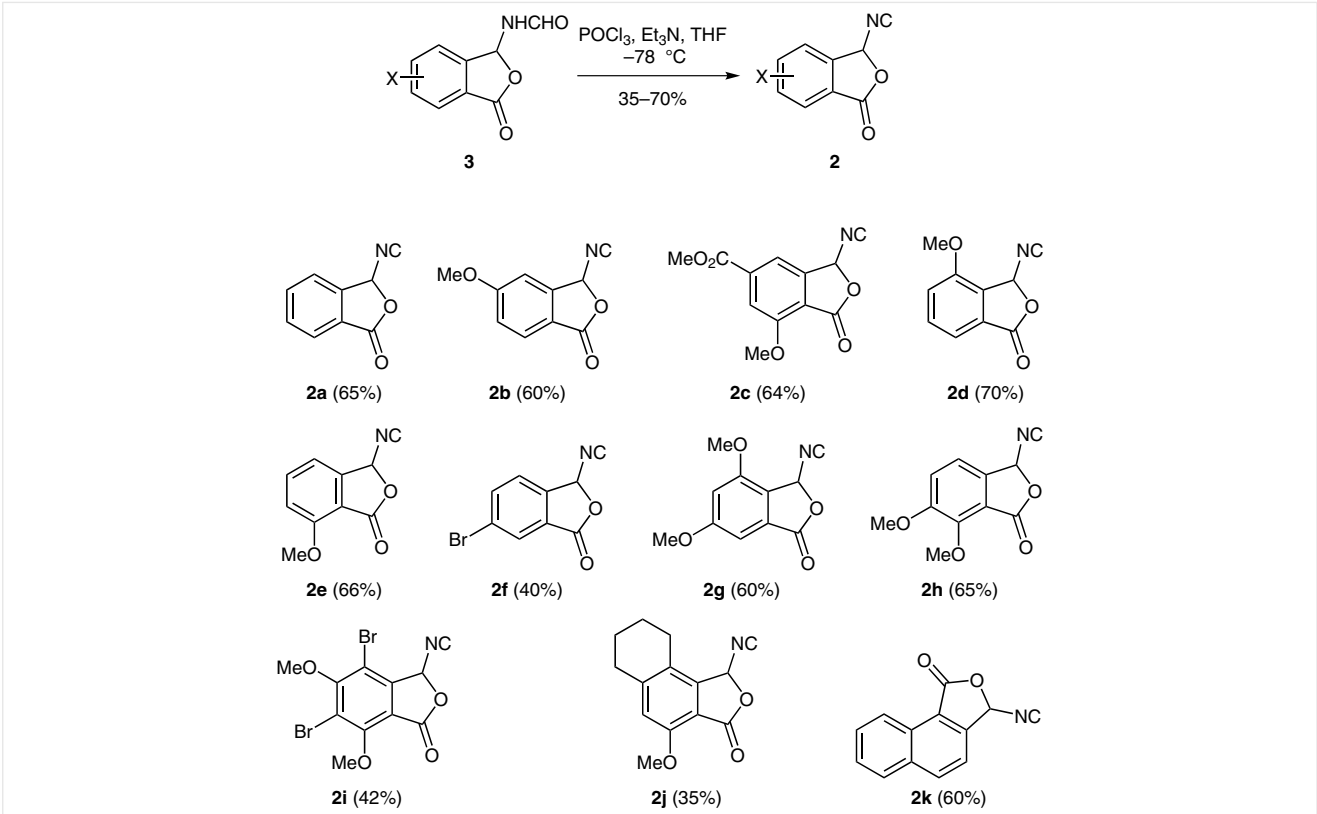
Scheme 2 Synthesis of 3-(formylamino)isobenzofuran-1(3*H*)-ones from phthalaldehydic acids

ing **4a** with neat formamide at 80 °C. The structure was confirmed by X-ray crystallographic analysis (see the Supporting Information). Both ^{1}H and ^{13}C NMR spectra of **3a** displayed complex splitting pattern due to the presence of two inseparable *cis* and *trans* rotamers in a 1:2 ratio (see the Supporting Information for analysis of the spectra). Two sharp IR bands near 1684 and 1763 cm^{-1} respectively correspond to CHO group and γ-lactone ring. Following the optimized conditions, twelve 3-(formylamino)isobenzofuran-1(3*H*)-ones **3a**–**l** were prepared (Scheme 2) from phthalaldehydic acids **4** in 45–90% yields. All the synthesized 3-(formylamino)isobenzofuran-1(3*H*)-ones have similar NMR patterns for formylamino units as that of the parent compound **3a**.

Having established of the synthesis of the 3-(formylamino)isobenzofuran-1(3*H*)-ones **3**, we undertook their conversion into the proposed isocyanides **2**. Exploratory studies with the parent 3-(formylamino)isobenzofuran-1(3*H*)-one (**3a**) involved a number of dehydrating agents [i.e., $POCl_3$, Py;[8] CBr_4, Ph_3P, Et_3N; $Cl_3COCO_2CCl_3$, Et_3N;[9] $POCl_3$, *i*-Pr_2NH;[10] $PhOPOCl_2$, Et_3N;[11] TMSCN, MsOH, Et_3N; Burgess reagent;[12] Tf_2O, Et_3N[13]]. Among the reagents examined, the Burgess reagent and triflic anhydride/triethylamine provided **2a** (X = H), but in very low yields; in all other cases, intractable mixtures were obtained. However, the use of freshly distilled triethylamine and phosphoryl chloride in anhydrous tetrahydrofuran at –78 °C and careful workup furnished the desired 3-isocyanoisobenzofuran-1(3*H*)-one (**2a**) in 65% yield (Scheme 3). The band at 2163 cm^{-1} in the IR spectrum clearly indicated the presence of isocyano group in the compound.

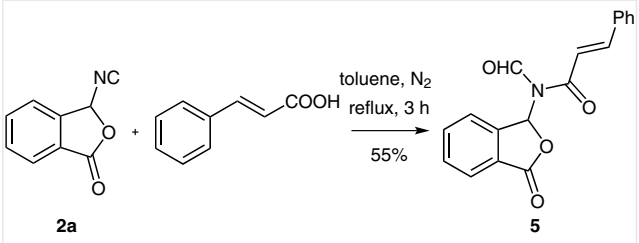
Isocyanide **2a** was further characterized chemically by its reaction with cinnamic acid. As expected,[14] it furnished 3-[formyl(3-phenylprop-2-enoyl)amino]isobenzofuran-1(3*H*)-one (**5**) (Scheme 4).

Following the conditions optimized for **2a**, 3-isocyanoisobenzofuran-1(3*H*)-ones **2a**–**k** were successfully prepared (Scheme 3). For the substrates with methoxy substituents **2b**,**d**,**e**,**g**,**h**, yields of the transformations are greater than those for substrates containing bromine **2f**,**i**. Surprisingly, 3-(formylamino)-6-nitroisobenzofuran-1(3*H*)-one (**3f**) could not be converted into its isocyanide under these conditions. Perhaps, nitro group induced increased acidity of C3–H of the isocyanide thus resulting in its dimerization or polymerization. This explanation seems to be in line with observations that the halogenated 3-isocyanoisobenzofuran-1(3*H*)-ones **2f** and **2i** are relatively unstable. These halogenated 3-isocyanoisobenzofuran-1(3*H*)-ones substantially polymerize at room temperature on standing for a



Scheme 3 3-Isocyanoisobenzofuran-1(3*H*)-ones from 3-(formylamino)isobenzofuran-1(3*H*)-ones

long time (~7 d), whereas sterically crowded 3-isocyano-4-methoxyisobenzofuran-1(3*H*)-one is highly stable at room temperature.



Scheme 4 Reaction of **2a** with cinnamic acid

Next, we explored the reactivity of the 3-isocyanoisobenzofuran-1(3*H*)-ones towards the Hauser annulation. Since the 3-isocyanoisobenzofuran-1(3*H*)-ones are susceptible to polymerization at room temperature, they were not used as limiting reagents in the annulation; they were used in excess, but at the end of the reaction no starting material recovered. The parent 3-isocyanoisobenzofuran-1(3*H*)-one (**2a**) first reacted with methyl acrylate in the presence of lithium *tert*-butoxide in tetrahydrofuran at –78 °C; the expected product, methyl 1,4-dihydroxynaphthalene-2-carboxylate (**6**)[15] was obtained in 31% yield. We briefly scrutinized several bases (Table 1) for improvement of the yields. Among the bases examined lithium *tert*-butoxide and sodium hydride were found to be quite attractive.

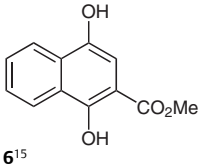
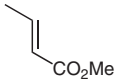
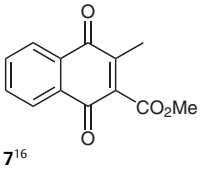
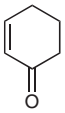
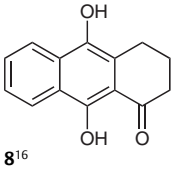
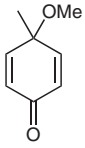
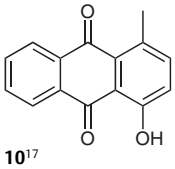
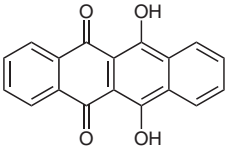
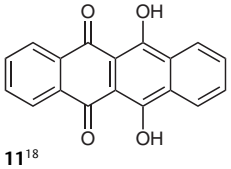
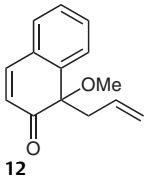
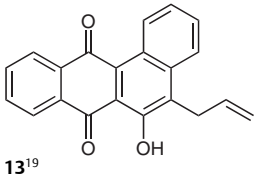
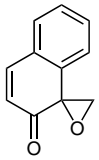
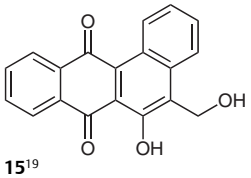
Table 1 Scrutiny of Bases and Solvents in the Annulation Reaction of 3-Isocyanoisobenzofuran-1(3*H*)-one (**2a**) and Methyl Acrylate

Entry	Conditions	Yield (%)
1	LiO*t*-Bu, THF, –78 °C to r.t., 8 h	46
2	LiO*t*-Bu, LiCl, –78 °C to r.t., 6–7 h	36
3	KO*t*-Bu, DMSO, r.t., 30 min	mixture
4	KO*t*-Bu, THF, –78 °C to r.t., 8 h	35
5	NaH, THF, –78 °C to r.t., 8 h	38
6	DBU, MeCN, 0 °C to r.t., 7 h	polymer
7	LDA, THF, –78 °C to r.t., 7 h	polymer
8	LiHMDS, THF, –78 °C to r.t., 7 h	polymer

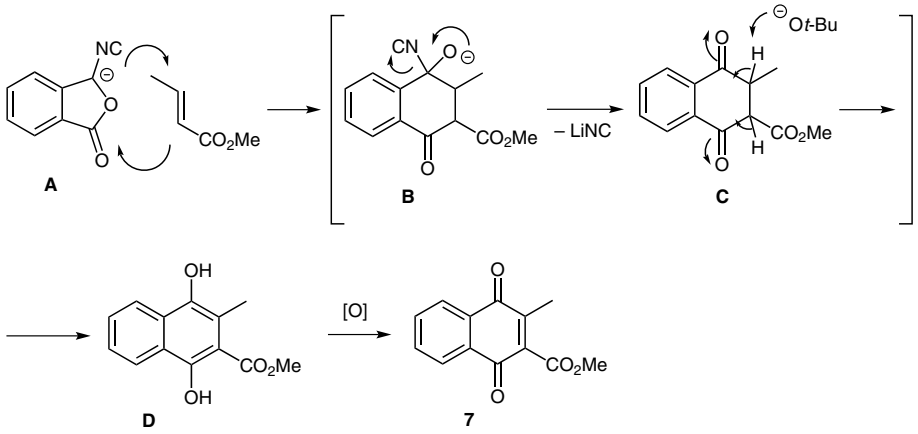
Substrate variation resulted in seven annulation products with moderate yields (Table 2). Annulation of **2a** with methyl crotonate similarly provided the corresponding aerial oxidized product **7**[16] in 36% yield (Scheme 5). The deprotonated isocyanide **A** undergoes Michael addition followed by Dieckmann cyclization to give **B** which collapses to diketone **C**. Proton abstraction via base of **C** resulted in

aromatized product **D** which on aerial oxidation furnished compound **7**. In case of cyclohexenone as the acceptor, expected product **8**,[16] contaminated with its dehydrogenated form, was isolated. With cyclohexadienone **9**, the yield of the annulation product **10**[17] was 23%. Expectedly, the product **11**[18] was obtained from 1,4-naphthoquinone in 35% yield. Hauser annulation reaction of **2a** with naphthalenone

Table 2 Annulation Reactions with 3-Isocyanoisobenzofuran-1(3*H*)-one (**2a**) or 3-Cyanoisobenzofuran-1(3*H*)-one (**1a**)

Entry	Acceptor	Product	Yield (%)	
			From **2a**	From **1a**[b]
1		 **6**[15]	31	68
2		 **7**[16]	36	73
3		 **8**[16]	46	75
4	 **9**	 **10**[17]	23	88
5		 **11**[18]	35	58
6	 **12**	 **13**[19]	56	97[b]
7	 **14**	 **15**[19]	48	88[b]

[a] Refers to isolated yields.
[b] From cited reference.



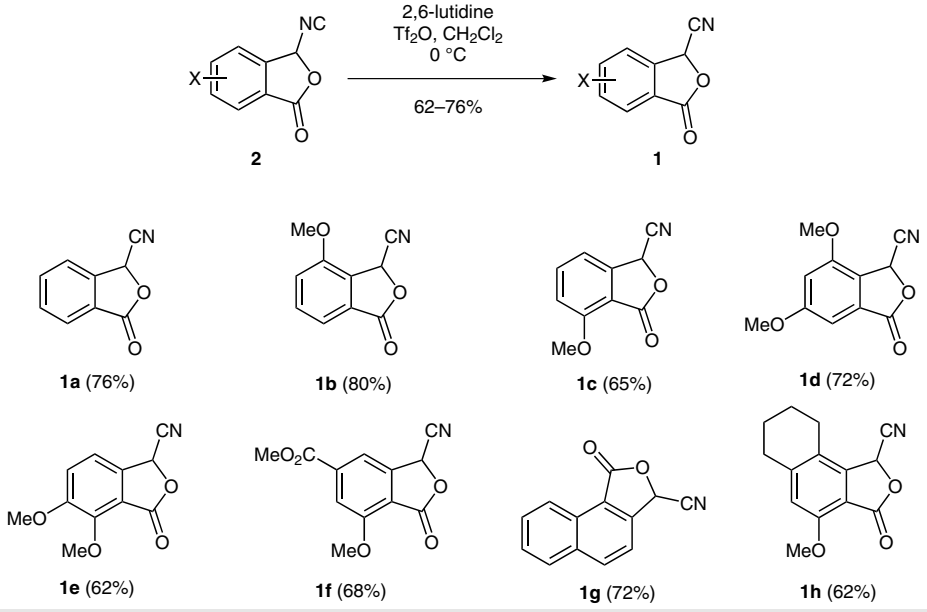
Scheme 5 Mechanism of annulation of isocyanide **2a** with methyl crotonate

12 and spiro[naphthalene-1(2*H*),2′-oxiran]-2-one **14** produced angucycline (**13**)[19] and 5-(hydroxymethyl)angucycline (**15**)[19] in 56 and 48% yields, respectively.

It appears from Tables 1 and 2 and earlier studies[20] that further improvement in the efficiency of the annulations can be made by rigorous examination of the base and reaction conditions.

To complement the efficiency of 3-isocyanoisobenzofuran-1(3*H*)-ones **2** as Hauser donors, we thought of their rearrangement to 3-cyanoisobenzofuran-1(3*H*)-ones **1**, already proven for their efficacy. Isomerization of organic isocyanides to their cyanides is generally conducted by thermal processes or metal salt catalyzed reactions.[21] Thermogravimetric analysis (TGA) of the parent 3-isocyanoisobenzofuran-1(3*H*)-one (**2a**) showed an endothermic peak at 150 °C; we attempted flash vacuum pyrolysis (FVP) of **2a** without success. We then examined Lewis acid catalyzed rearrangements following the studies of glycosyl isocyanides. Different Lewis acids[15] [e.g., ZnI_2, $Cu(OAc)_2$, $AlCl_3$, $FeCl_3$, TMSOTf, TBDMSCl, $PdCl_2$] and bases [e.g., DBU, Ag_2CO_3] in various solvents were used for the rearrangement of **2a**, but all these attempts were unsuccessful in producing the desired 3-cyanoisobenzofuran-1(3*H*)-one (**1a**). Finally, reaction with 2,6-lutidine followed by triflic anhydride at 0 °C gave 3-cyanoisobenzofuran-1(3*H*)-one (**1a**) in very good yield (Scheme 6).

The reaction was also carried out with combinations of several bases (pyridine, 2,6-lutidine, 2,4,6-collidine, Et_3N) with different acid anhydrides (TFAA, Tf_2O). While 2,6-lutidine with trifluoroacetic anhydride resulted in **1a** in trace



Scheme 6 Rearrangement of 3-isocyanoisobenzofuran-1(3*H*)-ones to 3-cyanoisobenzofuran-1(3*H*)-ones

amounts, 2,4,6-collidine with triflic anhydride gave **1a** in 35% yield. However, 2,6-lutidine a better base giving **1a** in 76% yield (Table 3). The reaction was also carried out with trifluoroacetic anhydride and 2,6-lutidine, but **1a** was obtained in trace amounts only.

Table 3 Scrutiny of Bases and Solvents in the Rearrangement of 3-Isocyanoisobenzofuran-1(3*H*)-one (**2a**) to 3-Cyanoisobenzofuran-1(3*H*)-one (**1a**)

Entry	Conditions	Yield(%)
1	Et_3N, TFAA, 0 °C, 10 h	0
2	Et_3N, Tf_2O, 0 °C, 10 h	0
3	pyridine, Tf_2O, 0 °C, 10 h	0
4	2,6-lutidine, TFAA, 0 °C	trace
5	2,6-lutidine, Tf_2O, 0 °C, 6 h	76
6	2,4,6-collidine, Tf_2O, 0 °C, 10 h	35

Under the optimized conditions, 3-isocyanoisobenzofuran-1(3*H*)-ones **2a**,**c**–**e**,**g**,**h**,**j**,**k** underwent smooth rearrangement to 3-cyanoisobenzofuran-1(3*H*)-ones **1a**–**h**[5c,22,29] (Scheme 6). To further extend the scope of the reaction and gain insight into the mechanism, we examined the reactivity of isocyanides, such as 4-toluenesulfonylmethyl isocyanide (TosMIC), *tert*-butyl isocyanide, ethyl isocyanoacetate, and phenyl isocyanide, under these conditions. Interestingly, these isocyanides resisted rearrangement to their corresponding cyano derivatives. In some cases, intractable mixtures of products were obtained.

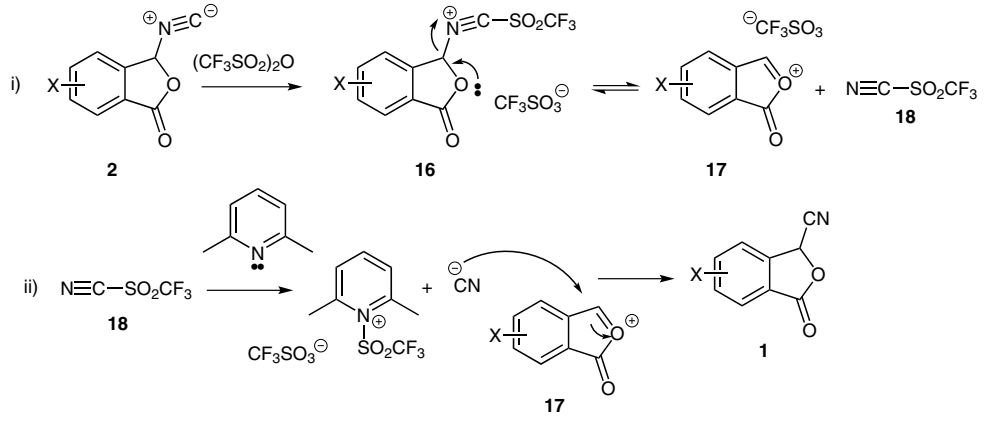
The mechanism of this isomerization can be explained as follows. Triflic anhydride reacts first with 3-isocyanoisobenzofuran-1(3*H*)-one **2** to produce activated nitrenium ion **16**, which then fragments into oxacarbenium ion **17** and triflyl cyanide (**18**). Cyanide ion, generated from triflyl cyanide by the reaction with 2,6-lutidine, then attacks the oxacarbenium ion **17** to furnish 3-cyanoisobenzofuran-1(3*H*)-one **1** (Scheme 7). The failure of the isomerization of 4-toluenesulfonylmethyl isocyanide, *tert*-butyl isocyanide, or ethyl isocyanoacetate indirectly supports the mechanism. The initial loss of the isocyanide from the substrates to form the corresponding carbenium (cf. 17) is not promoted by any group/atom.

In conclusion, the 3-isocyanoisobenzofuran-1(3*H*)-ones were prepared in two simple steps from phthalaldehydic acids. The 3-isocyanoisobenzofuran-1(3*H*)-ones can be rearranged to the established 3-cyanoisobenzofuran-1(3*H*)-ones using triflic anhydride and 2,6-lutidine. This preparation of 3-cyanoisobenzofuran-1(3*H*)-ones is free from the use of toxic cyanides. Moreover, the 3-isocyanoisobenzofuran-1(3*H*)-ones undergo Hauser annulation with Michael acceptors in low yields. Their efficacy in the annulation has been compared with those of established 3-cyanoisobenzofuran-1(3*H*)-ones.

Melting points are uncorrected. IR spectra were recorded on a Thermo Nicolet Nexus 870 FT-IR spectrophotometer using KBr pellets. Only the characteristic, strong and medium IR bands are presented. ^1H and ^{13}C NMR spectra of the samples in the indicated solvents were recorded on a 200 MHz or 400 MHz spectrometer (Bruker) with residual $CHCl_3$ and DMSO-d_6 as the internal standard. Mass spectra were taken using a VG Autospec M mass spectrometer. Dry solvents used for reactions were purified, before use, according to standard protocols. All solvents for chromatography were distilled prior to use. Columns were prepared with silica gel (60–120 or 230–400 mesh).

Annulation Reaction 6–8,10,11,13,15; General Procedure

To a stirred solution of LiO*t*-Bu (3.20 mmol) in THF (10 mL) at –78 °C ($CHCl_3$–liq N_2 bath) under an inert atmosphere was added a solution of isocyanophthalide (1.0 mmol) in THF (5 mL). The resulting yellowish solution was stirred at –78 °C for 25 min, after which a solution of a Michael acceptor (1.0–1.5 equiv unless otherwise stated) in THF (5 mL) was added. The cooling bath was removed after ca. 1 h at –78 °C and the mixture was brought to r.t. over a period of 1 h and stirred for a further 2–6 h. The reaction was then quenched with 10% aq NH_4Cl (15 mL) and the resulting solution was concentrated. The residue was



Scheme 7 Proposed mechanism for the isomerization of isocyanides to cyanides

diluted with EtOAc (50 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 25 mL). The combined extracts were washed with H_2O (15 mL) and brine (15 mL), dried (anhyd Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel) or by recrystallization to obtain the pure product.

3-(Formylamino)isobenzofuran-1(3*H*)-ones 3a–l; General Procedure

A stirred solution of a phthalaldehydic acid **4** (6.00 mmol) dissolved in neat formamide (3 mL/mmol) was heated for 4 h (unless otherwise stated) at 80–100 °C with an argon balloon fitted with a condenser. The reaction was monitored by TLC. When the reaction was complete, the mixture was extracted with EtOAc (3 × 40 mL) and the combined organic extracts were washed with brine (6 × 20 mL) and dried (Na_2SO_4). Removal of the solvent gave a residue that was purified by column chromatography (60–120 mesh size, CH_2Cl_2–MeOH, 95:5) or by recrystallization (MeOH).

3-Isocyanoisobenzofuran-1(3*H*)-ones 2a–k; General Procedure

To a stirred solution of 3-(formylamino)isobenzofuran-1(3*H*)-one **3**, dissolved in dry THF (8 mL/mmol) was added freshly distilled Et_3N (5 equiv) at –78 °C and the mixture was stirred for 10 min. Then freshly distilled $POCl_3$ (1.3 equiv) was added to the mixture at –78 °C and the mixture was maintained this temperature for a further 0.5 h and then allowed to reach r.t. and stirred for 1.5 h (TLC monitoring). When the starting material had been consumed, the mixture was quenched with aq $NaHCO_3$. Solvent was evaporated under reduced pressure, the residue was extracted with Et_2O (3 × 30 mL), and the combined extracts were washed with H_2O (2 × 20 mL) and brine. After removal of Et_2O, the resulting residue was purified by column chromatography.

3-Cyanoisobenzofuran-1(3*H*)-ones 1a–h; General Procedure

To a stirred solution of 3-isocyanoisobenzofuran-1(3*H*)-one **2** dissolved in dry CH_2Cl_2 (10 L/mol) at 0 °C was added 2,6-lutidine (2 equiv) and the mixture was stirred for 20 min at 0 °C. Tf_2O (2 equiv) was added then dropwise at this temperature. The resulting mixture was stirred for 6 h at r.t. The reaction was quenched with 1 M HCl and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with H_2O (20 mL) and brine (20 mL). Purification was performed by column chromatography or by preparative TLC.

4,5-Dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-carbonitrile (1e)

Following the general procedure using **2h** (100 mg, 0.45 mmol), CH_2Cl_2 (15 mL), and 2,6-lutidine (0.10 mL, 0.91 mmol); 0 °C, 15 min, followed by Tf_2O (0.14 mL, 0.91 mmol). Work up used 1 M HCl (1 × 10 mL), and the CH_2Cl_2 extracts were washed with H_2O (3 × 10 mL) and brine (1 × 10 mL). Removal of CH_2Cl_2 under reduced pressure gave a residue that was purified by column chromatography to give **1e** (62 mg, 62%) as a white solid; mp 120–122 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 3.6 Hz, 2 H), 5.96 (s, 1 H), 4.13 (s, 3 H), 3.95 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.1, 164.5, 148.8, 135.1, 120.1, 117.7, 116.5, 113.2, 64.0, 62.7, 57.0.

HRMS (ES+): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{10}NO_4$: 220.0611; found: 220.0615.

1-Oxo-1,3-dihydronaphtho[1,2-*c*]furan-3-carbonitrile (1g)

Following the general procedure using **2k** (100 mg, 0.48 mmol), CH_2Cl_2 (15 mL), and 2,6-lutidine (0.11 mL, 0.96 mmol); 0 °C, 15 min, followed by Tf_2O (0.15 mL, 0.96 mmol). Workup as for **1e** with purification by column chromatography gave **1g** (72 mg, 72%) as a white solid; mp 123–125 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.94 (d, *J* = 8.4 Hz, 1 H), 8.31 (d, *J* = 8.4 Hz, 1 H), 8.05 (d, *J* = 8.4 Hz, 1 H), 7.81 (t, *J* = 7.4 Hz, 1 H), 7.75 (t, *J* = 7.6 Hz, 1 H), 7.69 (d, *J* = 8.4 Hz, 1 H), 6.16 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0, 143.4, 137.5, 134.5, 130.3, 129.1, 129.0, 128.9, 123.7, 119.6, 118.3, 114.0, 65.6.

HRMS (ES+): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_8NO_2$: 210.0556; found: 210.0559.

3-Isocyanoisobenzofuran-1(3*H*)-one (2a)

Following the general procedure using **3a** (500 mg, 2.8 mmol), THF (20 mL), and Et_3N (1.2 mL, 8.4 mmol) then $POCl_3$ (0.35 mL, 3.6 mmol). Purification by column chromatography gave **2a** (290 mg, 65%) as a yellow solid; mp 60–62 °C.

IR (KBr): 2163, 1792, 1723, 1561, 1465, 1054, 1011, 747 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 7.2 Hz, 1 H), 7.86 (t, *J* = 7.4 Hz, 1 H), 7.63–7.45 (m, 2 H), 6.53 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7, 164.9, 142.7, 135.7, 131.9, 126.2, 124.7, 122.9, 78.3.

HRMS (ES+): *m*/*z* [M + H]$^+$ calcd for $C_9H_6NO_2$: 160.0399; found: 160.0401.

3-Isocyano-5-methoxyisobenzofuran-1(3*H*)-one (2b)

Following the general procedure using **3b** (300 mg, 1.45 mmol), THF (15 mL), Et_3N (0.6 mL, 4.35 mmol), and $POCl_3$ (0.2 mL, 1.88 mmol). Purification by column chromatography gave **2b** (165 mg, 60%) as a yellow solid; mp 63–65 °C.

IR (KBr): 2322, 1724, 1621, 1435, 1285, 1140, 750 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 8.8 Hz, 1 H), 7.18 (dd, *J* = 2, 8.4 Hz, 1 H), 7.12 (d, *J* = 2 Hz, 1 H), 6.42 (s, 1 H), 3.96 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6, 166.1, 165.1, 145.9, 128.0, 119.4, 116.9, 107.0, 77.9, 56.5.

HRMS (ES+): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_8NO_3$: 190.0505; found: 190.0510.

Methyl 3-Isocyano-7-methoxy-1-oxo-1,3-dihydroisobenzofuran-5-carboxylate (2c)

Following the general procedure using **3c** (356 mg, 1.34 mmol), THF (15 mL), Et_3N (0.6 mL, 4.03 mmol), and $POCl_3$ (0.16 mL, 1.74 mmol). Purification by column chromatography gave **2c** (212 mg, 64%) as a yellow solid; mp 72–74 °C.

IR (KBr): 2320, 1758, 1718, 1612, 1440, 1336, 1244, 1106, 1051, 769 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (s, 1 H), 7.77 (s, 1 H), 6.48 (s, 1 H), 4.09 (s, 3 H), 4.01 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4, 164.7, 163.8, 158.5, 145.1, 139.1, 115.3, 115.1, 114.7, 77.5, 56.7, 53.1.

HRMS (ES+): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{10}NO_5$: 248.0559; found: 248.0562.

3-Isocyano-4-methoxyisobenzofuran-1(3*H*)-one (2d)

Following the general procedure using **3d** (400 mg, 1.93 mmol), THF (17 mL), Et_3N (0.8 mL, 5.7 mmol), and $POCl_3$ (0.24 mL, 2.5 mmol). Purification by column chromatography gave **2d** (255 mg, 70%) as a yellow solid; mp 81–83 °C.

IR (KBr): 2356, 1723, 1576, 1445, 1060, 101121, 740 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.65 (t, *J* = 7.8 Hz, 1 H), 7.48 (d, *J* = 7.4 Hz, 1 H), 7.24 (d, *J* = 8 Hz, 1 H), 6.44 (s, 1 H), 3.99 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7, 164.2, 154.8, 133.8, 129.8, 126.4, 117.4, 116.8, 76.9, 56.1.

HRMS (ES+): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_8NO_3$: 190.0505; found: 190.0509.

3-Isocyano-7-methoxyisobenzofuran-1(3*H*)-one (2e)

Following the general procedure using **3e** (450 mg, 2.17 mmol), THF (15 mL), Et_3N (0.9 mL, 6.5 mmol), and $POCl_3$ (0.3 mL, 2.8 mmol). Purification by column chromatography gave **2e** (270 mg, 66%) as a yellow solid; mp 70–72 °C.

IR (KBr): 2320, 1726, 1619, 1452, 1292, 1140, 756 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.76 (t, *J* = 8 Hz, 1 H), 7.23 (d, *J* = 7.6 Hz, 1 H), 7.09 (d, *J* = 8.4 Hz, 1 H), 6.42 (s, 1 H), 4.01 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.0, 164.8, 159.0, 145.4, 138.2, 114.3, 113.8, 112.2, 77.5, 56.6.

HRMS (ES+): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_8NO_3$: 190.0505; found: 190.0510.

6-Bromo-3-isocyanoisobenzofuran-1(3*H*)-one (2f)

Following the general procedure using **3g** (250 mg, 0.9 mmol), THF (10 mL), Et_3N (0.4 mL, 2.9 mmol), and $POCl_3$ (0.11 mL, 1.17 mmol). Purification by column chromatography gave **2f** (93 mg, 40%) as a yellow solid; mp 63–65 °C.

IR (KBr): 2326, 1710, 1655, 1529, 1435, 1386, 1300, 1278, 1143, 708 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.52 (s, 1 H), 7.65 (d, *J* = 8.2 Hz, 1 H), 8.00 (d, *J* = 8.2 Hz, 1 H), 8.13 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.6, 154.7, 145.3, 137.2, 128.7, 127.8, 123.9, 123.1, 77.8.

HRMS (ES+): *m*/*z* $[M + H]^+$ calcd for $C_9H_5BrNO_2$: 237.9504; found: 237.9508 and 239.9488.

3-Isocyano-4,6-dimethoxyisobenzofuran-1(3*H*)-one (2g)

Following the general procedure using **3h** (500 mg, 2.1 mmol), THF (15 mL), Et_3N (0.88 mL, 6.3 mmol), and $POCl_3$ (0.26 mL, 2.73 mmol). Purification by column chromatography gave **2g** (278 mg, 60%) as a yellow solid; mp 72–74 °C.

IR (KBr): 2360, 1785, 1720, 1561, 1535, 1455, 1050, 865, 747 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.92 (d, *J* = 2 Hz, 1 H), 6.75 (d, *J* = 1.8 Hz, 1 H), 6.38 (s, 1 H), 3.95 (s, 3 H), 3.88 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2, 164.9, 164.1, 155.7, 127.7, 123.4, 106.1, 99.6, 77.2, 56.4, 56.3.

HRMS (ES+): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{10}NO_4$: 220.0611; found: 220.0617.

3-Isocyano-6,7-dimethoxyisobenzofuran-1(3*H*)-one (2h)

Following the general procedure using **3j** (600 mg, 2.23 mmol), THF (10 mL), Et_3N (0.99 mL, 7.1 mmol), and $POCl_3$ (0.28 mL, 2.89 mmol). Purification by column chromatography gave **2h** (150 mg, 65%) as a yellow solid; mp 63–65 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.35 (s, 2 H), 6.39 (s, 1 H), 4.01 (s, 3 H), 3.93 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.5, 154.6, 148.8, 135.1, 120.0, 117.3, 116.5, 77.4, 62.7, 57.6.

HRMS (ES+): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{10}NO_4$: 220.0611; found: 220.0615.

4,6-Dibromo-3-isocyano-5,7-dimethoxyisobenzofuran-1(3*H*)-one (2i)

Following the general procedure using **3i** (350 mg, 0.9 mmol), THF (10 mL), Et_3N (0.37 mL, 2.7 mmol), and $POCl_3$ (0.11 mL, 1.17 mmol). Purification by column chromatography gave **2i** (135 mg, 42%) as a yellow solid; mp 63–65 °C.

IR (KBr): 2300, 1727, 1610, 1452, 1292, 1189, 756, 556 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.27 (s, 1 H), 4.17 (s, 3 H), 4.02 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7, 162.7, 162.0, 157.5, 142.9, 139.3, 118.2, 114.1, 77.8, 63.4, 61.3.

HRMS (ES+): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_8Br_2NO_4$: 375.8821; found: 375.8824, 375.8827, 377.8806.

1-Isocyano-4-methoxy-6,7,8,9-tetrahydronaphtho[1,2-*c*]furan-3(1*H*)-one (2j)

Following the general procedure using **3k** (450 mg, 1.7 mmol), THF (15 mL), Et_3N (0.72 mL, 5.1 mmol), and $POCl_3$ (0.21 mL, 2.21 mmol) with workup as for **2h**. Purification by column chromatography gave pure **2j** (146 mg, 35%) as a yellow solid; mp 65–67 °C.

IR (KBr): 2322, 1717, 1621, 1522, 1435, 1332, 1300, 1285, 1140, 750 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.27 (s, 1 H), 6.79 (s, 1 H), 3.95 (s, 3 H), 2.91–2.87 (m, 4 H), 2.04–1.79 (s, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9, 156.5, 154.0, 148.7, 142.1, 123.9, 113.8, 109.3, 77.65, 56.14, 30.46, 24.22, 22.19, 22.07.

HRMS (ES+): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{14}NO_3$: 244.0974; found: 244.0980.

3-Isocyanonaphtho[1,2-*c*]furan-1(3*H*)-one (2k)

Following the general procedure using **3l** (550 mg, 2.41 mmol), THF (15 mL), Et_3N (1.01 mL, 7.26 mmol), and $POCl_3$ (0.3 mL, 2.21 mmol) with workup as for **2h**. Purification by column chromatography gave **2k** (300 mg, 60%) as a yellow solid; mp 63–65 °C.

IR (KBr): 2322, 1717, 1621, 1522, 1435, 1332, 1300, 1285, 1140, 750 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.89 (d, *J* = 8.4 Hz, 1 H), 8.28 (d, *J* = 8.4 Hz, 1 H), 8.02 (d, *J* = 8.4 Hz, 1 H), 7.80–7.69 (m, 3 H), 6.57 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.1, 165.4, 144.1, 137.5, 134.7, 130.2, 129.0, 128.9, 128.7, 123.9, 119.9, 118.4, 78.2.

HRMS (ES+): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_8NO_2$: 210.0556; found: 210.0562.

***N*-(3-Oxo-1,3-dihydroisobenzofuran-1-yl)formamide (3a)**

Following the general procedure using **4a** (1 g, 6.7 mmol) and formamide (10 mL) at 80 °C for 3 h. Workup used EtOAc (3 × 60 mL), H_2O (3 × 20 mL), and brine (20 mL) to give **3a** (1.06 g, 90%) as a white solid; mp 112–115 °C.

IR (KBr): 1763, 1684, 1515, 1394, 1063 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ (mixture of rotamers) = 9.37 (d, *J* = 9.2 Hz, 2 H, trans), 9.03 (t, *J* = 10.4 Hz, 1 H, cis), 8.47 (d, *J* = 10.4 Hz, 1 H, cis), 8.28 (s, 2 H, trans), 7.87–7.65 (m, 6 H, cis + trans), 7.105 (d, *J* = 9.6 Hz, 1 H, trans), 6.97 (d, *J* = 10.0 Hz, 1 H, cis).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.1, 165.9, 162.8, 146.4, 145.9, 135.3, 135.2, 131.1, 130.9, 126.9, 126.8, 125.2, 125.2, 124.3, 124.0, 85.2, 79.5.

HRMS (ES+): *m*/*z* $[M + H]^+$ calcd for $C_9H_8NO_3$: 178.0505; found: 178.0509.

***N*-(6-Methoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)formamide (3b)**

Following the general procedure using 3-hydroxy-5-methoxyisobenzofuran-1(3*H*)-one[23] (500 mg, 2.78 mmol) and formamide (10 mL) at 80 °C for 4 h. Workup used EtOAc (3 × 60 mL), H_2O (3 × 20 mL), and brine (20 mL) followed by column chromatography to give **3b** (460 mg, 80%) as a white solid; mp 102–104 °C.

IR (KBr): 3312, 2908, 2857, 1560, 1442, 1233, 713 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ (mixture of rotamers) = 9.34 (d, *J* = 9.2 Hz, 2 H, trans), 8.99 (t, *J* = 10.8 Hz, 1 H, cis), 8.44 (t, *J* = 10.8 Hz, 1 H, cis), 8.27 (s, 2 H, trans), 7.76 (d, *J* = 9.6 Hz, 3 H, cis + trans), 7.23–7.14 (m, 5 H, cis + trans), 7.00 (d, *J* = 9.6 Hz, 2 H, trans), 6.86 (d, *J* = 10.4 Hz, 1 H, cis), 3.87 (s, 6 H, cis + trans).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.7, 165.0, 162.6, 149.2, 126.8, 126.7, 118.9, 118.4, 118.3, 108.1, 107.9, 84.3, 78.5, 86.6.

HRMS (ES+): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{10}NO_4$: 208.0611; found: 208.0618.

Methyl 3-(Formylamino)-7-methoxy-1-oxo-1,3-dihydroisobenzofuran-5-carboxylate (3c)

Following the general procedure using methyl 3-hydroxy-7-methoxy-1-oxo-1,3-dihydroisobenzofuran-5-carboxylate[24] (500 mg, 2.10 mmol) and formamide (10 mL) at 100 °C for 6 h. Workup used EtOAc (3 × 60 mL), H_2O (3 × 20 mL), and brine (20 mL) followed by column chromatography to give **3c** (478 mg, 86%) as a yellowish solid; mp 133–135 °C.

IR (KBr): 3312, 2908, 2857, 1560, 1442, 1233, 710.

^{1} H NMR (400 MHz, DMSO-d_6): δ (mixture of rotamers) = 9.33 (d, *J* = 9.4 Hz, 2 H, trans), 8.95 (t, *J* = 10.6 Hz, 1 H, cis), 8.42 (d, *J* = 10.8 Hz, 2 H, cis), 8.21 (s, 2 H, trans), 7.72 (s, 1 H, cis + trans), 7.63 (d, *J* = 2.2 Hz, 5 H, cis + trans), 7.01 (d, *J* = 9 Hz, 2 H, trans), 6.89 (d, *J* = 10.0 Hz, 1 H, cis), 3.99 (s, 3 H, cis + trans), 3.91 (s, 3 H, cis + trans).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.1, 165.5, 164.0, 163.9, 162.5, 156.2, 156.1, 129.7, 126.1, 125.6, 105.8, 99.6, 83.7, 79.8, 78.0, 66.3, 56.8, 56.7.

HRMS (ES+): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{12}NO_6$: 266.0665; found: 266.0669.

***N*-(7-Methoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)formamide (3d)**

Following the general procedure using 3-hydroxy-4-methoxyisobenzofuran-1(3*H*)-one[25] (600 mg, 3.33 mmol) and formamide (10 mL) at 100 °C for 3 h. Workup used EtOAc (3 × 60 mL), H_2O (3 × 20 mL), and brine (20 mL) followed by column chromatography to give **3d** (605 mg, 88%) as a white solid; mp 132–134 °C.

IR (KBr): 3312, 2908, 2857, 1560, 1442, 1233, 710 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ (mixture of rotamers) = 8.89 (d, *J* = 9.2 Hz, 2 H, trans), 8.65 (d, *J* = 8.8 Hz, 2 H, cis), 8.29–8.25 (m, 3 H, cis + trans), 8.13 (s, 2 H, trans), 7.50 (t, *J* = 8 Hz, 3 H, cis + trans), 7.23 (d, *J* = 8 Hz, 6 H, cis + trans), 6.39 (d, *J* = 9.2 Hz, 2 H, trans), 6.10 (d, *J* = 8 Hz, 1 H, cis), 3.84 (s, 6 H, cis + trans).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.9, 163.5, 160.6, 155.0, 133.5, 133.0, 131.7, 128.9, 117.4, 117.3, 116.2, 115.9, 81.9, 85.9, 85.8.

HRMS (ES+): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{10}NO_4$: 208.0611; found: 208.0620.

***N*-(4-Methoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)formamide (3e)**

Following the general procedure using 3-hydroxy-7-methoxyisobenzofuran-1(3*H*)-one (500 mg, 2.77 mmol) and formamide (10 mL) at 100 °C for 12 h. Workup used EtOAc (3 × 60 mL), H_2O (3 × 20 mL), and brine (20 mL) followed by column chromatography to give **3e** (400 mg, 70%) as a white solid; mp 126–128 °C.

IR (KBr): 3312, 2908, 2857, 1560, 1442, 1233, 710 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ (mixture of rotamers) = 9.31 (d, *J* = 9.2 Hz, 2 H, trans), 8.98 (d, *J* = 8.8 Hz, 2 H, cis), 8.45 (d, *J* = 10.8 Hz, 1 H, cis), 8.29 (s, 2 H, trans), 7.78 (t, *J* = 8 Hz, 3 H, cis + trans), 7.26–7.12 (m, 6 H, cis + trans), 6.95 (d, *J* = 9.2 Hz, 2 H, trans), 6.85 (d, *J* = 8 Hz, 1 H, cis), 3.95 (s, 6 H, cis + trans).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.5, 165.7, 162.6, 158.2, 148.9, 137.5, 115.6, 115.3, 113.8, 113.3, 83.6, 77.9, 56.4.

HRMS (ES+): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{10}NO_4$: 208.0611; found: 208.0620.

***N*-(5-Nitro-3-oxo-1,3-dihydroisobenzofuran-1-yl)formamide (3f)**

Following the general procedure using 3-hydroxy-6-nitroisobenzofuran-1(3*H*)-one[26] (850 mg, 4.35 mmol) and formamide (15 mL) at 100 °C for 6 h. Workup used EtOAc (3 × 60 mL), H_2O (3 × 20 mL), and brine (20 mL) followed by column chromatography to give pure **3f** (830 mg, 86%) as a white solid; mp 123–125 °C.

IR (KBr): 3310, 2900, 2857, 1560, 1447, 1252, 708 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ (mixture of rotamers) = 9.45 (d, *J* = 9.2 Hz, 2 H, trans), 9.06 (t, *J* = 10.8 Hz, 1 H, cis), 8.64–8.59 (m, 3 H, cis + trans), 8.53–8.47 (m, 3 H, cis + trans), 8.30, 8.28 (2 × s, 3 H, cis + trans), 8.00 (d, *J* = 8 Hz, 1 H, cis), 7.93 (d, *J* = 8.4 Hz, 2 H, trans), 7.18 (d, *J* = 8.8 Hz, 2 H, trans), 7.12 (d, *J* = 10.4 Hz, 1 H, cis).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 179.8, 166.2, 165.9, 162.8, 151.9, 153.3, 149.8, 129.9, 129.8, 128.6, 128.6, 126.2, 125.7, 120.2, 120.2, 85.4, 79.9, 79.5.

HRMS (ES+): *m*/*z* $[M + H]^+$ calcd for $C_9H_7N_2O_5$: 223.0356; found: 223.0360.

***N*-(5-Bromo-3-oxo-1,3-dihydroisobenzofuran-1-yl)formamide (3g)**

Following the general procedure using 6-bromo-3-hydroxyisobenzofuran-1(3*H*)-one[27] (350 mg, 1.54 mmol) and formamide (7 mL) at 100 °C for 6 h. Workup used EtOAc (3 × 60 mL), H_2O (3 × 20 mL), and brine (20 mL) followed by column chromatography to give **3g** (252 mg, 65%) as a yellow solid; mp 88–90 °C.

IR (KBr): 3312, 2908, 2857, 1560, 1442, 1233, 708 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ (mixture of rotamers) = 9.32 (d, *J* = 9.2 Hz, 2 H, trans), 8.96–8.81 (m, 3 H, cis + trans), 8.46 (t, *J* = 9.2 Hz, 1 H, cis), 8.23, 8.21, 8.13 (3 × s, 2 H, cis + trans), 7.94 (s, 2 H, trans), 7.95–7.91 (m, 2 H, cis + trans), 7.63 (dd, *J* = 9.2 Hz, 8 Hz, 2 H, cis + trans), 7.07–6.91 (m, 3 H, cis + trans).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.7, 167.1, 165.9, 162.8, 146.9, 145.6, 138.0, 137.9, 131.5, 129.9, 129.6, 129.4, 129.4, 128.3, 127.9, 127.8, 126.7, 126.5, 126.2, 123.9, 85.3, 84.7, 79.7, 79.3.

HRMS (ES+): *m*/*z* [M + H]$^+$ calcd for $C_9H_7BrNO_3$: 255.9610; found: 255.9615.

***N*-(5,7-Dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)formamide (3h)**

Following the general procedure using 3-hydroxy-4,6-dimethoxyisobenzofuran-1(3*H*)-one[28] (600 mg, 2.85 mmol) and formamide (10 mL) at 100 °C for 6 h. Workup used EtOAc (3 × 60 mL), H_2O (3 × 20 mL), and brine (20 mL) followed by column chromatography to give **3h** (580 mg, 85%) as a white solid; mp 132–133 °C.

IR (KBr): 3320, 2890, 2855, 1567, 1452, 1234, 710, 694 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ (mixture of rotamers) = 9.24 (d, *J* = 9.2 Hz, 2 H, trans), 8.92 (t, *J* = 10.8 Hz, 1 H, cis), 8.42 (d, *J* = 10.8 Hz, 1 H, cis), 8.22 (s, 2 H, trans), 6.96–6.84 (m, 8 H, cis + trans), 3.84 (s, 6 H, cis + trans).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.1, 165.5, 164.0, 163.9, 162.5, 156.3, 156.2, 129.7, 126.1, 125.7, 105.9, 99.6, 83.8, 79.8, 78.0, 60.4, 56.8, 56.7.

HRMS (ES+): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{12}NO_5$: 238.0716; found: 238.0762.

***N*-(5,7-Dibromo-4,6-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)formamide (3i)**

Following the general procedure using 4,6-dibromo-3-hydroxy-5,7-dimethoxyisobenzofuran-1(3*H*)-one (350 mg, 0.95 mmol) and formamide (5 mL) at 100 °C for 4 h. Workup used EtOAc (3 × 60 mL), H_2O (3 × 20 mL), and brine (20 mL) followed by column chromatography to give **3i** (265 mg, 70%) as a yellowish solid; mp 126–128 °C.

IR (KBr): 3310, 2900, 2857, 1560, 1447, 1252, 725, 708 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ (mixture of rotamers) = 9.26 (d, *J* = 9.2 Hz, 2 H, trans), 8.86 (t, *J* = 9.0 Hz, 1 H, cis), 8.49 (d, *J* = 10.8 Hz, 1 H, cis), 8.28, 8.27 (2 s, 3 H, cis + trans), 6.89–6.85 (m, 3 H, cis + trans), 3.98 (s, 6 H, cis + trans), 3.87 (s, 6 H, cis + trans).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.8, 164.9, 164.4, 162.6, 160.6, 160.4, 156.1, 147.6, 146.8, 117.4, 117.2, 116.2, 115.9, 108.1, 107.7, 84.4, 79.8, 79.7, 79.5, 79.2, 78.9, 63.2, 61.5.

HRMS (ES+): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{10}Br_2NO_5$: 393.8926; found: 393.8928, 395.8910.

***N*-(4,5-Dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)formamide (3j)**

Following the general procedure using opianic acid (1 g, 4.76 mmol) and formamide (15 mL) at 120 °C for 6 h. Workup used EtOAc (3 × 60 mL), H_2O (3 × 20 mL), and brine (20 mL) followed by column chromatography to give **3j** (855 mg, 76%) as a white solid; mp 152–154 °C.

IR (KBr): 3320, 2890, 2855, 1567, 1452, 1234, 710, 694 cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ (mixture of rotamers) = 9.27 (d, *J* = 9.2 Hz, 2 H, trans), 8.92 (t, *J* = 10.8 Hz, 1 H, cis), 8.42 (d, *J* = 10.8 Hz, 1 H, cis), 8.26 (s, 2 H, trans), 7.49 (d, *J* = 8.4 Hz, 3 H, cis + trans), 7.28 (t, *J* = 9.4 Hz, 3 H, cis + trans), 6.94 (d, *J* = 9.4 Hz, 2 H, trans), 6.78 (d, *J* = 10 Hz, 1 H, cis), 3.90 (s, 3 H, cis + trans), 3.86 (s, 3 H, cis + trans).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 166.6, 166.3, 165.9, 162.8, 153.9, 153.8, 147.5, 147.4, 138.9, 138.6, 120.7, 119.4, 119.3, 119.1, 84.0, 79.8, 78.2, 62.2, 57.4.

HRMS (ES+): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{12}NO_5$: 238.0716; found: 238.0726.

***N*-(1-Oxo-1,3-dihydronaphtho[1,2-*c*]furan-3-yl)formamide (3l)**

Following the general procedure using 3-hydroxy-3*H*-naphtho[1,2-*c*]furan-1-one (500 mg, 2.5 mmol) and formamide (8 mL) at 120 °C for 3 h; Workup used EtOAc (3 × 60 mL), H_2O (3 × 20 mL), and brine (20 mL) followed by column chromatography to give **3l** (350 mg, 62%) as a light yellow solid; mp 126–128 °C.

IR: 3310, 2900, 2857, 1560, 1447, 1252, 725, 708 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ (mixture of rotamers) = 8.84–8.78 (m, 3 H, cis + trans), 8.39–8.31 (m, 3 H, cis + trans), 8.21–8.13 (m, 3 H, cis + trans), 7.89 (t, *J* = 9.0 Hz, 2 H, trans), 7.79–7.67 (m, 2 H, cis + trans), 6.82 (d, *J* = 10.8 Hz, 1 H, cis), 6.71 (d, *J* = 10.8 Hz, 2 H, trans), 6.55 (d, *J* = 10.8 Hz, 1 H, cis).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.0, 169.7, 169.4, 149.7, 148.6, 147.9, 136.3, 136.2, 136.1, 134.3, 129.8, 129.7, 129.5, 128.7, 128.6, 128.6, 128.2, 128.1, 123.3, 122.3, 121.8, 121.3, 121.1, 121.0, 120.9, 98.0, 91.8, 89.1.

HRMS (ES+): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{10}NO_3$: 228.0661; found: 228.0670.

3-[Formyl(3-phenylprop-2-enoyl)amino]isobenzofuran-1(3*H*)-one (5)[29]

To a solution of **2a** (30 mg, 0.19 mmol) dissolved in dry toluene (5 mL) in a round-bottom flask fitted with a N_2 balloon was added cinnamic acid (14 mg, 0.09 mmol). The mixture was heated at 110 °C for 3 h. After complete disappearance of **2a**, toluene was removed under reduced pressure. The residue was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with H_2O (20 mL) and brine (20 mL). The residue was purified by column chromatography to provide **5** (31 mg, 55%) as a yellow oil.

^1H NMR (200 MHz, $CDCl_3$): δ = 9.25 (s, 1 H), 8.01–7.51 (m, 10 H), 6.81 (d, *J* = 15.2 Hz, 1 H), 6.52 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 209.9, 166.3, 153.3, 150.0, 149.4, 138.4, 136.3, 129.8, 128.5, 127.4, 127.2, 125.3, 124.8, 121.5, 115.7, 108.0.

Methyl 1,4-Dihydroxynaphthalene-2-carboxylate (6)[15]

Following the general procedure using **2a** (159 mg, 1 mmol), methyl acrylate (95 mg, 1.1 mmol), Li*O*t-Bu (256 mg, 3.2 mmol), and THF (7 mL). Purification by column chromatography gave pure **6** (67 mg, 31%) as a yellow solid; mp 193–195 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.55 (s, 1 H), 8.40 (d, *J* = 8.4 Hz, 1 H), 8.13 (d, *J* = 8.4 Hz, 1 H), 7.68–7.55 (m, 2 H), 7.11 (s, 1 H), 5.04 (br s, 1 H), 3.98 (s, 3 H).

Methyl 3-Methyl-1,4-dioxo-1,4-dihydronaphthalene-2-carboxylate (7)[16]

Following the general procedure using **2a** (159 mg, 1 mmol), methyl crotonate (110 mg, 1.1 mmol), LiO*t*-Bu (256 mg, 3.2 mmol), and THF (12 mL) afforded **7** (82 mg, 36%) as a light yellow solid; mp 96–98 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.37 (d, *J* = 8.4 Hz, 1 H), 8.04 (d, *J* = 8.2 Hz, 1 H), 7.70–7.44 (m, 2 H), 3.99 (s, 3 H), 2.52 (s, 3 H).

9,10-Dihydroxy-3,4-dihydroanthracen-1(2*H*)-one (8)[16]

Following the general procedure using **2a** (159 mg, 1 mmol), cyclohex-2-en-1-one (106 mg, 1.1 mmol), LiO*t*-Bu (256 mg, 3.2 mmol), and THF (12 mL) afforded **8** (105 mg, 46%) as a yellow solid; mp 172–174 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 13.85 (s, 1 H), 8.39 (d, *J* = 8.2 Hz, 1 H), 8.04 (d, *J* = 8.4 Hz, 1 H), 7.68–7.45 (m, 2 H), 2.95 (t, *J* = 8.0 Hz, 2 H), 2.76–2.59 (m, 2 H), 2.40 (t, *J* = 8.0 Hz, 2 H).

1-Hydroxy-4-methylanthracene-9,10-dione (10)[17]

Following the general procedure using **2a** (159 mg, 1 mmol), 4-methoxy-4-methylcyclohexa-2,5-dien-1-one (**9**, 134 mg, 1.1 mmol), LiO*t*-Bu (256 mg, 3.2 mmol), and THF (12 mL) afforded **10** (54 mg, 23%) as a white solid; mp 173–175 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.19 (s, 1 H), 8.32–8.25 (m, 2 H), 7.83–7.74 (m, 2 H), 7.50 (d, *J* = 17.6 Hz, 1 H), 7.22 (d, *J* = 17.6 Hz, 1 H), 2.75 (s, 3 H).

6,11-Dihydroxytetracene-5,12-dione (11)[18]

Following the general procedure using **2a** (159 mg, 1 mmol), naphthalene-1,4-dione (173 mg, 1.1 mmol), LiO*t*-Bu (256 mg, 3.2 mmol), and THF (12 mL) afforded **11** (100 mg, 35%) as a yellow solid; mp above 300 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 15.19 (s, 2 H), 8.52–8.47 (m, 4 H), 7.90–7.74 (m, 4 H).

5-Allyl-6-hydroxytetraphene-7,12-dione (13)[19]

Following the general procedure using **2a** (159 mg, 1 mmol), **12** (235 mg, 1.1 mmol), LiO*t*-Bu (256 mg, 3.2 mmol), and THF (12 mL) afforded **13** (175 mg, 56%) as a red solid; mp 182–184 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.91 (s, 1 H), 9.44 (d, *J* = 8.8 Hz, 1 H), 8.22 (d, *J* = 8 Hz, 2 H), 7.90 (d, *J* = 8.4 Hz, 1 H), 7.81–7.73 (m, 2 H), 7.56–7.48 (m, 2 H), 6.10–6.03 (m, 1 H), 5.10–5.07 (m, 2 H), 3.95 (d, *J* = 5.5 Hz, 2 H).

6-Hydroxy-5-(hydroxymethyl)tetraphene-7,12-dione (15)[19]

Following the general procedure using **2a** (159 mg, 1 mmol), **14** (190 mg, 1.1 mmol), LiO*t*-Bu (256 mg, 3.2 mmol), and THF (12 mL) afforded **15** (145 mg, 48%) as a red solid; mp 180–182 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.25 (d, *J* = 8.8 Hz, 1 H), 8.14–8.09 (m, 3 H), 7.94–7.85 (m, 2 H), 7.62 (t, *J* = 7.6 Hz, 1 H), 7.50 (t, *J* = 7.6 Hz, 1 H), 5.22 (s, 1 H), 4.93 (s, 2 H).

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Supporting Information

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