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One-pot synthesis of benzofurans *via* heteroannulation of benzoquinones

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Abstract: Three different reactions were explored leading to the synthesis of various benzofurans. All reactions took place under AcOH catalysis in a one-pot manner. As a result, benzoquinone derivatives underwent heteroannulation with either itself or cyclohexanones to produce furanylidene-benzofuran or benzofuran structures, respectively.

Keywords: benzofuran, furanylidene-benzofuran, benzoquinone, heteroannulation, one-pot reaction

Introduction

Heterocyclic compounds possessing the benzofuran core [1], of either natural or synthetic origin [2], are very important due to their exhibition of various biological activities. This has led to numerous investigations to design procedures for the synthesis of benzofuran based structures [3,4] and to study their biological behavior [5] as antioxidant [6], anticancer [7], antimicrobial [8], antitumor [9], and immunomodulatory [10] agents. As a result, the extensive physiological properties and the high natural occurrence of benzofuran derivatives have resulted in their use as versatile biodynamic and useful therapeutic agents. Important natural examples include moracins [11], cicerfuran [12], and conocarpan [13], while bufuralol [14], amiodarone [15], and ailanthoidol [16] are representative derivatives of biologically active synthetic benzofuran molecules (Fig. 1).

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The broad spectrum of biochemical activities of various benzofurans has led to many investigations to prepare specific target structures from natural sources or *via* synthetic methods. Several arylbenzofurans were extracted from the stem bark [17], root bark [18], and leaves [19] of various mulberry trees, some of which were also prepared *via* multistep syntheses [20,21]. Notable methods for the synthesis of benzofurans include metal-free cyclization of *ortho*-hydroxystilbenes mediated by hypervalent iodine reagents [22], Ru-catalyzed isomerization [23] of appropriate precursors [24], cross-coupling of alkali-metal salts of silanols with aromatic halides [25], Pd-catalyzed addition of potassium aryltrifluoroborates to aliphatic nitriles [26], Sonogashira coupling of *O*-iodoanisoles with terminal alkynes followed by electrophilic cyclizations [27], and one-pot Pd-catalyzed coupling of *ortho*-bromophenols with enolizable ketones [28].

In the framework of our studies on the synthesis of various heterocyclic systems [29-31], and in continuation of our program on the use of cyclohexenone derivatives **1a**-**c** in the synthesis [32-34], we decided to take advantage of the reactivity of cyclohexenone derivatives for possible coupling with benzoquinone (BQ), as shown in Scheme 1 for the heteroannulation of **1a** with BQ. This work resulted in the one-pot synthesis of benzofuran and furanylidene-benzofuran systems **2**-**4** in PhMe/AcOH (4:1) medium.

Results and discussion

Confident in the application of [3+2] heteroannulations in the preparation of benzofuran structures, we first targeted the synthesis of **2**. For this purpose, we reacted **1a** with BQ in a refluxing PhMe/AcOH mixture, in which 81% of **2** was obtained after 24 h (Scheme 1). It is noteworthy that the synthesis of **2** was previously reported *via* a three-step process taking 6 days and achieving an overall yield of about 80% [35], whereas we could access **2** through a single step reaction (Scheme 2). Mechanistically, the reaction is probably going through a formal [3+2] process, and presumably a cyclic transition state (**1a**-BQH$^+$) is involved. Protonation of BQ in acidic conditions and formation of

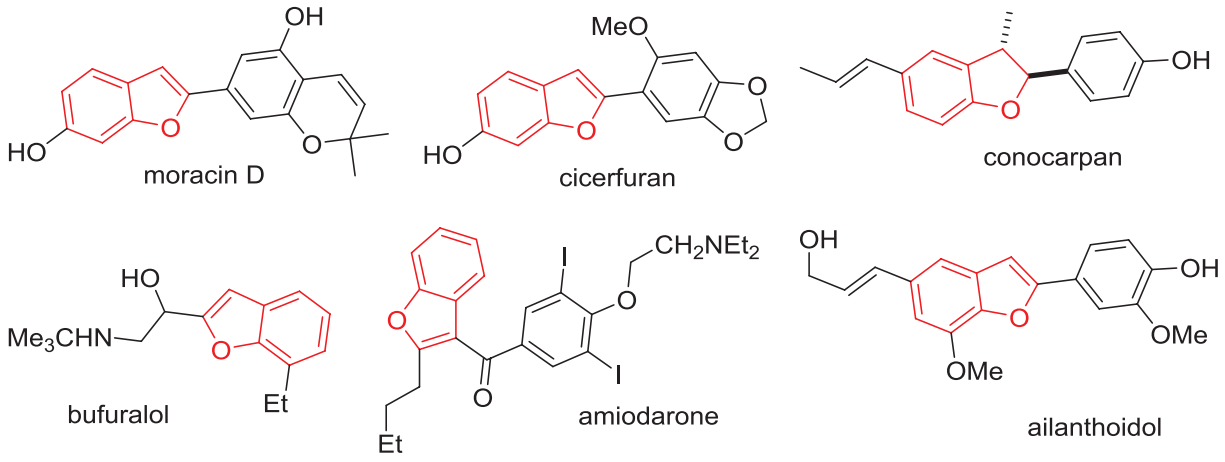
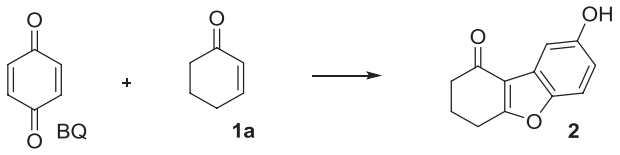


Figure 1 Important bioactive benzofuran containing structures



Scheme 1 One-pot synthesis of **2**

BQH^+ [36] and its participation in hetrocycloadditions have precedence [37].

To gain some understanding of the process, we replaced **1a** with **1b**. Treatment of BQ with **1b** (Table 1) in refluxing PhMe/AcOH solution for 3 days gave a complex mixture of products from which *m*-cresol, hydroquinone (HQ), and low yields of product **3** were identified (entry 1). The presence of a HQ skeleton in the structure of **3** and the formation of *m*-cresol as a side product suggested that a redox process could be involved. Therefore, similar reactions were performed replacing BQ with HQ. When HQ and **1b** were used, no formation of **3** was detected (entry 2), while a repeat of each reaction in the absence of **1b** was also unsuccessful (entries 3-4). In contrast, a mixture of BQ and HQ produced a 70% yield of **3** after an 18 h reflux in PhMe/AcOH (entry 5). It is noteworthy that **3** belongs to the group of furanylidene-benzofuran heterocycles which contain both benzofuran and additional lactone moieties and are important for their pigment [38] and biochemical [39] properties.

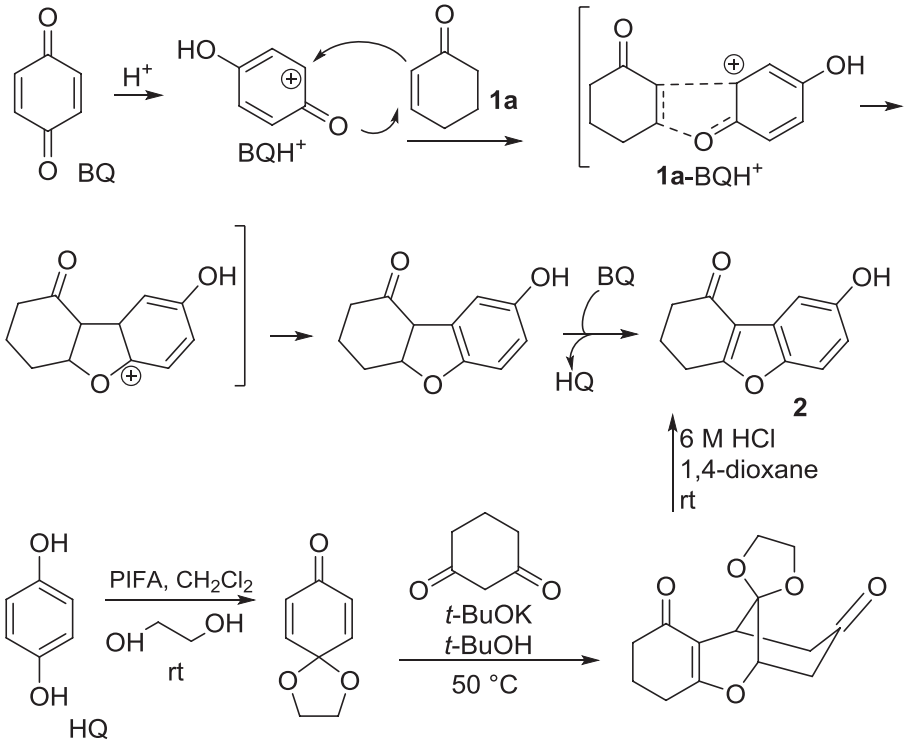
To further understand the process, we repeated the reactions in the presence of CD_3CO_2D, in which the same results were obtained (entry 6), proving the lack of the participation of acetic acid in the structure of the product. Similarly, use of cyclohexa-1,4-diene (CHD), as a radical scavenger [40], halted the reaction completely, supporting the inclusion of a redox process in the reaction (entry 7). Changing the solvent (entries 8-12) or the acid reagent (entries 13-16) did not improve the results. The use of two other BQ derivatives (2,5-dimethylcyclohexa-2,5-diene-1,4-dione, 2,5-DMBQ, entry 17 and 2,6-dimethylcyclohexa-2,5-diene-1,4-dione, 2,6-DMBQ, entry 18) gave no respective products, as would be expected from their more electron rich nature.

To confirm that a hydrogen donor source such as **1b** or HQ is needed for the reaction to proceed, we replaced **1b** with either **1c** or **1d** and repeated the reactions in the absence of HQ (Scheme 3). Thus, with 2:1 mixtures of BQ and **1c** (or **1d**) no detectable reactions were observed.

Based on the results, a pathway was proposed in which BQ is first protonated to BQH^+ [36]. This hypothetical intermediate is stabilized *via* ring opening to a conjugated oxo-bis-enone moiety, which in turn is attacked by water to form the hydroxyethylidene-furanone intermediate. Further oxidation of this intermediate by BQ and its coupling with the resulting HQ, followed by the final lactonization, gives **3** (Scheme 4).

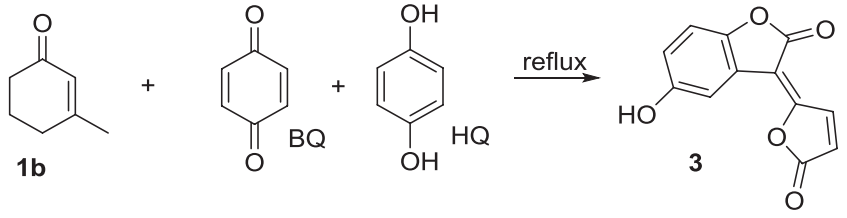
The structure of **3** was identified based on its NMR spectra. In ^1H NMR, the presence of two doublets and one doublet of doublets signals at about 6.8-7.2 ppm was in accordance with the HQ unit, while two doublet signals at 8.4 and 7.0 ppm were indicative of the unsaturated lactone ring. Similarly, DEPT-135, COSY, HSQC, and APT experiments supported the formation of the suggested structure. To confirm, a single crystal of **3** was prepared and subjected to X-ray crystallographic experiments. Fig. 2 clearly supports the assignment.

Based on these results, we decided to design a pathway in which a similar combination of BQ structures would occur *via* an elimination reaction as opposed to a redox process. For this purpose, we selected 2,6-dichlorobenzoquinone ($BQCl_2$), which is more susceptible to protonation



Scheme 2 Stepwise *vs* one-pot synthesis of **2**

Table 1 Optimization of the synthesis of **3** using **1b**



Entry	1b (equiv.)	BQ (equiv.)	HQ (equiv.)	Conditions	Time (h)	Yield (%)[a]
1	1.0	2.5	0.0	AcOH, PhMe	72	15
2	1.0	0.0	2.5	AcOH, PhMe	72	0
3	0.0	1.0	0.0	AcOH, PhMe	72	0
4	0.0	0.0	1.0	AcOH, PhMe	72	0
5	0.0	2.0	1.0	AcOH, PhMe	18	70
6	0.0	2.0	1.0	CD_3CO_2D, PhMe	18	70
7	0.0	2.0	1.0	CHD, AcOH, PhMe	72	0
8	0.0	2.0	1.0	AcOH, $CHCl_3$	18	0
9	0.0	2.0	1.0	AcOH, H_2O	18	0
10	0.0	2.0	1.0	AcOH, mesitylene	18	55
11	0.0	2.0	1.0	AcOH, xylene	18	53
12	0.0	2.0	1.0	AcOH, benzene	18	33
13	0.0	2.0	1.0	CF_3CO_2H, PhMe	18	0
14	0.0	2.0	1.0	HCO_2H, PhMe	18	67
15	0.0	2.0	1.0	PTSA, PhMe	18	0
16	0.0	2.0	1.0	HCl, PhMe	18	0
17	0.0	2.0[b]	1.0	AcOH, PhMe	18	0
18	0.0	2.0[c]	1.0	AcOH, PhMe	18	0

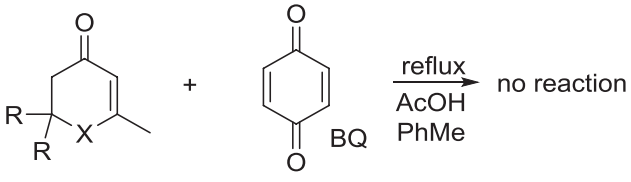
[a]Isolated yields. [b]BQ was replaced with 2,5-DMBQ. [c]BQ was replaced with 2,6-DMBQ.

[41], and has the potential to produce dibenzofurans, when reacted with ethyl 2-methyl-4-oxocyclohex-2-ene-1-carboxylate (Hagmann ester, **1e**). This would occur by taking advantage of a possible facile HCl elimination to couple the two reactants and reach a tricyclic dibenzofuran target structure (Scheme 5). As a result, a facile regioselective coupling was observed, giving **4**.

The mechanism of the reaction presumably goes through the formation of $BQCl_2H^+$. This species is formed upon treatment of the reactants with AcOH, while **1e** is also enolized to dienol **1e′** under the acidic conditions. Then, the enol **1e′** attacks the electron-poor $BQCl_2H^+$ to form **4′**. Rearrangement of the double bond to a more stable conjugated position promotes the ring closure and the process is followed by HCl elimination and a final dehydration/aromatization step to form **4** (Scheme 6). The structure of the product was elucidated with NMR spectroscopy techniques and was confirmed with X-ray crystallographic analysis (Fig. 3).

Conclusion

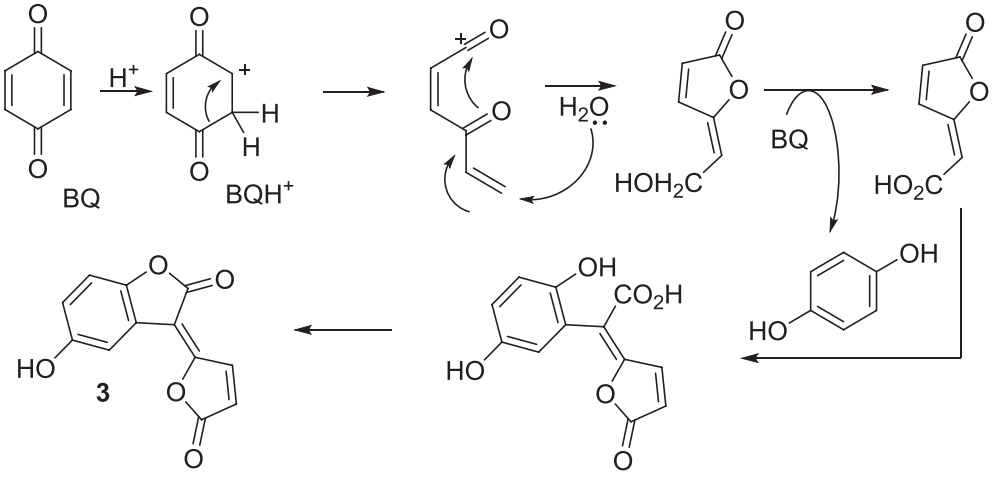
In summary, we successfully conducted the synthesis of benzofuran and furanylidene-benzofuran systems *via* the one-pot coupling of BQ with either itself or cyclohexenone under refluxing acidic conditions, using no coupling reagent. The benzofuran formation occurs either through [3+2] heteroannulation of the starting cyclohexenone moiety with BQ derivatives (in the case of **2** and **4**) or the "dimerization" of BQ (in the case of **3**), followed by either spontaneous oxidation (aromatization) or elimination (dehydration) steps. The procedures are clearly effective in producing the target compounds under inexpensive conditions, in shorter time periods and with fewer reaction steps when compared to the previous reports for known products [35]. Based on these results, we are currently developing the procedures to use a broader spectrum of reactants, such as phenols and thiophenols.



Scheme 3 Reactions in the presence of **1c-d**

Experimental

Melting points are uncorrected. FT-IR spectra were recorded using KBr disks on a Bruker Vector-22 spectrometer. NMR spectra were recorded at 400 MHz for ^{1}H NMR and 101 MHz for ^{13}C NMR on a Bruker Ascend 400 MHz spectrometer in DMSO-d_6 solutions using TMS as an internal standard reference. Chemical shift values (δ) are reported in ppm relative to the residual solvent signal in DMSO, while coupling constants (*J*) are given in Hz. Multiplicities are reported as s (singlet), d (doublet), dd (doublet of doublets), m (multiplet) and etc. Flash column chromatography was performed using silica gel 60 (0.035-0.070 mm particle size). Elemental analyses were performed using a Thermo Finnigan Flash EA 1112 instrument. LCMS analysis was carried out on a Waters ACQUITY UPLC system with a PDA and SQD2 electrospray detector and a Thermo Accucore C18 2.6 μm, 2.1 × 50 mm column. TLC experiments were carried out on pre-coated silica gel plates using hexanes/EtOAc as the eluent. Chemicals and starting materials were purchased from commercial sources.



Scheme 4 Mechanism of the synthesis of **3**

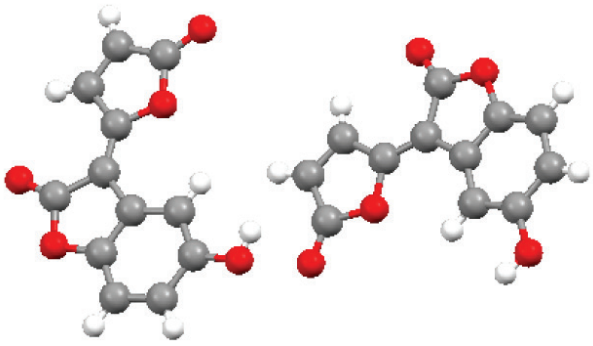
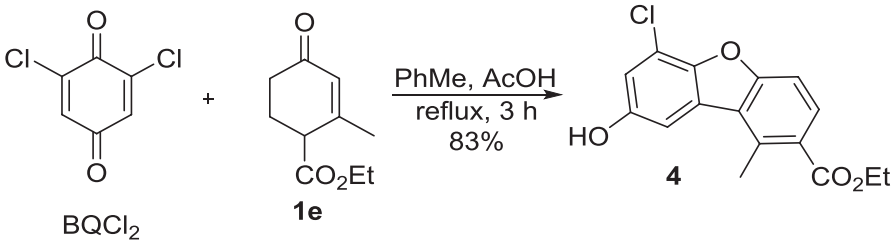


Figure 2 ORTEP representation of **3**, thermal ellipsoids set at the 40% probability level

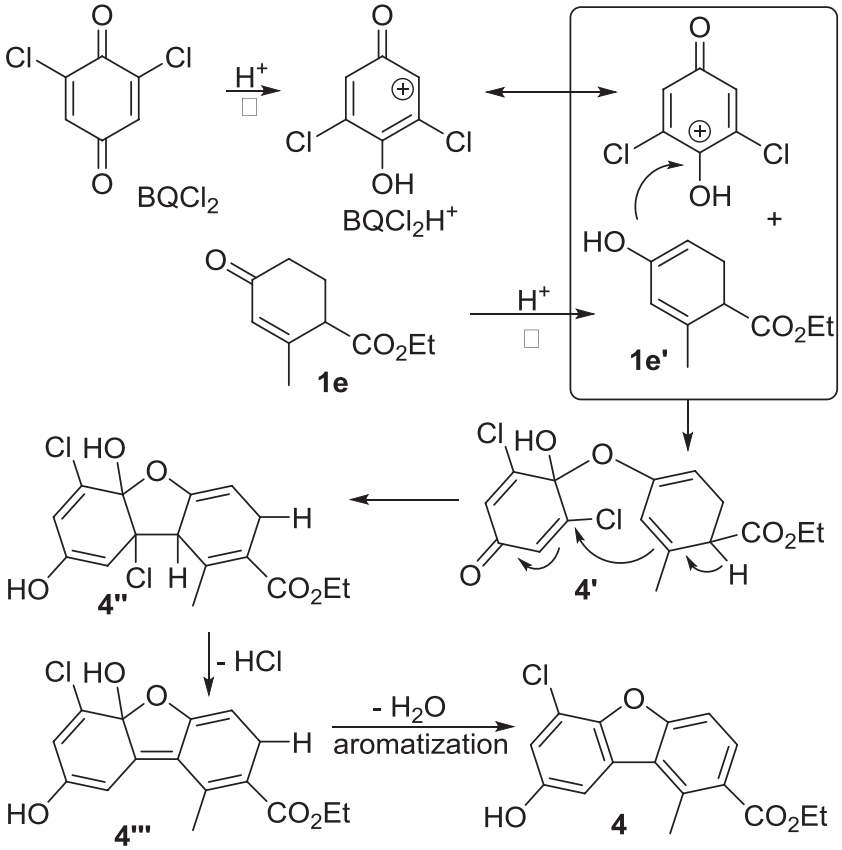
Product **2** [35] was known and identified by NMR spectra. Products **3** and **4** were new and were characterized by analysis of their ^{1}H NMR, ^{13}C NMR, IR, mass spectra, and X-ray crystallography.

Synthesis of 8-hydroxy-3,4-dihydrodibenzo[*b*,*d*]furan-1(2*H*)-one (2)

To a solution of PhMe (4.0 mL) and glacial AcOH (1.0 mL) was added **1a** (100 µL, 1.0 mmol) and benzoquinone (216 mg, 2.0 mmol) and the mixture was refluxed for 24 hours. Saturated aqueous $NaHCO_3$ (excess) was added



Scheme 5 Synthesis of **4**



Scheme 6 Mechanism of the synthesis of **4**

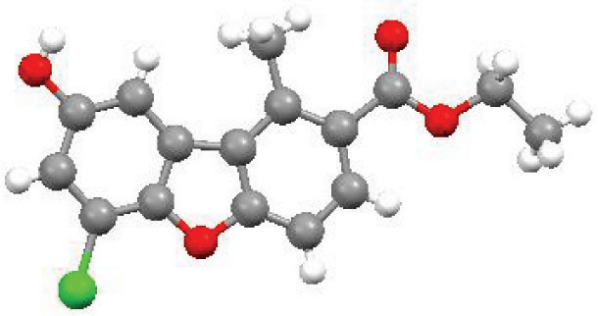


Figure 3 ORTEP representation of **4**, thermal ellipsoids set at the 40% probability level

to the mixture and the organic layer was diluted with EtOAc (10.0 mL). The organic layer was dried over Na_2SO_4 and after evaporation of the volatiles, the residue was purified with flash chromatography over silica gel using EtOAc/hexanes (1:5) to obtain **2**.

White crystals (81%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.40 (s, 1H), 7.43 (d, J = 9.0 Hz, 1H), 7.26 (d, J = 2.5 Hz, 1H), 6.75 (dd, J = 2.5, 9.0 Hz, 1H), 3.03-3.00 (m, 2H), 2.49-2.48 (m, 2H), 2.19-2.12 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 194.8, 172.5, 155.1, 148.3, 124.6, 115.9, 113.6, 112.2, 106.1, 33.8, 23.7, 22.4; MS: m/z 202 (M^+).

Synthesis of (*E*)-5-hydroxy-3-(5-oxofuran-2(5*H*)-ylidene) benzofuran-2(3*H*)-one (3)

To a solution of PhMe (4.0 mL) and glacial AcOH (1.0 mL) was added benzoquinone (216 mg, 2.0 mmol) and hydroquinone (110 mg, 1.0 mmol) and the mixture was refluxed for 18 hours. Saturated aqueous $NaHCO_3$ (excess) was added to the mixture and the organic layer was diluted with EtOAc (10.0 mL). The organic layer was dried over Na_2SO_4 and after evaporation of the volatiles, the residue was purified with flash chromatography over silica gel using EtOAc/hexanes (1:5) to obtain **3**.

Red crystals (70%); 210 °C (decomposes); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.65 (s, 1H), 8.43 (d, J = 5.5 Hz, 1H), 7.18 (d, J = 2.5 Hz, 1H), 7.10 (d, J = 8.5 Hz, 1H), 7.01 (d, J = 5.5 Hz, 1H), 6.85 (dd, J = 2.5, 8.5 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.0, 166.9, 155.4, 154.5, 146.9, 141.2, 125.2, 122.0, 119.2, 120.4, 111.1, 106.0; IR (KBr) ν 1064, 1466, 1766, 2922, 3467 cm^{-1}; MS: m/z 230 (M^+). Anal. Calcd for $C_{12}H_6O_5$: C, 62.62; H, 2.63. Found: C, 62.50; H, 2.75.

X-ray data for 3

$C_{12}H_6O_5$, M = 230.17 g/mol, triclinic system, space group P-1, a = 7.0075(7), b = 9.9741(7), c = 14.5706(12) Å, α=81.108(6), β = 79.856(8), γ=70.532(8), V = 940.10(15) Å^3, Z = 4, Dc = 1.626 g/cm-3, μ(Mo-Kα) = 0.129 mm^{-1}, crystal dimension of 0.1 × 0.1 × 0.1 mm. The X-ray data collection for **3** was performed on an Agilent Supernova Diffractometer. Data processing was done using *CrysAlisPro* (Agilent Technologies). The structure was solved by using SHELXS, and structure refinement was carried out with SHELXL [42]. The non-hydrogen atoms were refined anisotropically by full matrix least-squares on *F2* values to final R1 = 0.0822, *w*R2 = 0.2630, and S = 1.009 with 309 parameters using 4647 independent reflection (θ range = 3.19–29.65°). Hydrogen atoms were included on ideal positions using riding coordinates. Crystallographic data for **3** have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to The Director, CCDC-2046512, Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.

Synthesis of ethyl 6-chloro-8-hydroxy-1-methyldibenzo[b,d]furan-2-carboxylate (4)

To a solution of PhMe (4.0 mL) and glacial AcOH (1.0 mL) was added **1e** (160 μL, 1.0 mmol) and $BQCl_2$ (264 mg, 1.5 mmol) and the mixture was refluxed for 3 hours. Saturated aqueous $NaHCO_3$ (excess) was added to the mixture and the organic layer was diluted with EtOAc (10.0 mL). The organic layer was dried over Na_2SO_4 and after evaporation of the volatiles, the residue was purified with flash chromatography over silica gel using EtOAc/hexanes (1:5) to obtain **4.**

White crystals (83%); mp = 183-184 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.99 (s, 1H), 7.91 (d, J = 9.0, 1H), 7.58 (d, J = 9.0 Hz, 1H), 7.45 (d, J = 2.0 Hz, 1H), 7.06 (d, J = 2.0 Hz, 1H), 4.32 (q, J = 7.0 Hz, 2H), 2.88 (s, 3H), 1.35 (t, J = 7.0 Hz, 3H); ^{13}CNMR (101 MHz, DMSO-d_6) δ 167.3, 157.6, 154.7, 145.6, 136.8, 130.6, 126.2, 125.9, 123.9, 115.9, 116.0, 109.8, 107.9, 61.2, 17.3, 14.6 ; IR (KBr) ν 3344, 2853, 1681, 1258, 1073, 779 cm^{-1}; MS: m/z = 304 [M]$^+$. Anal. Calcd for $C_{16}H_{13}ClO_4$: C, 63.07; H, 4.30. Found: C, 63.25; H, 4.52.

X-ray data for 4

$C_{16}H_{13}ClO_4$, M = 304.71 g/mol, monoclinic system, space group $P2_1/c$, a = 12.0554(3), b = 7.2442(1), c = 15.3414(3) Å, β = 95.954(2), V = 1332.56(5) Å^3, Z = 4, Dc = 1.519 g/cm-3, μ(Cu-Kα) = 2.672 mm^{-1}, crystal dimension of 0.25 × 0.20 × 0.18 mm. The structure was solved using SHELXS and refined with SHELXL [40]. The non-hydrogen atoms were refined anisotropically by full matrix least-squares on *F2* values to final R1 = 0.0470, *w*R2 = 0.1360, and S = 1.025

with 193 parameters using 2792 independent reflection (θ range = 3.69–76.56°). Hydrogen atoms were inserted at ideal positions.

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Conflict of interest: Authors state no conflicts of interest.

Data availability statement: Crystallographic data for **4** have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to The Director, CCDC-2046513, Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk. All other data generated or analyzed during this study are included in this published article and its supplementary information file.

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