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A Convenient and Efficient Synthesis of 3-benzofuryl-substituted phthalides

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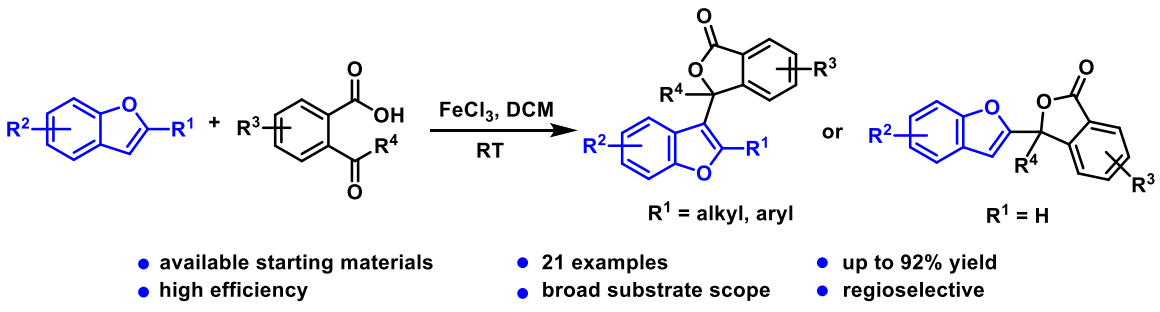
Abstract

A highly efficient and convenient procedure for straightforward synthesizing structurally diverse 3-benzofuryl-substituted phthalides is developed with moderate to excellent yields via cyclization reactions of benzofurans with 2-carbonyl-benzoic acid. The reaction features readily available starting materials, a broad scope, and a high atom economy. Besides, an interesting regioselective was observed in some cases.



Keywords: Phthalide, benzofuran, cyclization, heterocyclic

Introduction

The privileged heterocyclic phthalide scaffolds are widely available in natural products and pharmaceuticals.[1-3] Among various phthalides, 3-substituted phthalides have been proven to possess various biological activities.[2, 4-10] Representative examples include *n*-butylphthalide, which has been approved as an anti-ischemic stroke drug in China.[6] (±)-Catalpalactone exhibits specific cytotoxic and antisemitic activities.[11, 12] Vermistatin displays cytotoxic effects against cancer cells.[13] Plant growth inhibitors are displayed by (±)-Chrycolide which is obtained from the *Chrysanthemum coronarium*.[14] Isopestacin shows antifungal and antioxidant activities and is isolated from the endophytic fungus *Pestalotiopsis microspore*.[15, 16] Fluorescein is currently used as a diagnostic aid in clinical (Figure 1).[17]

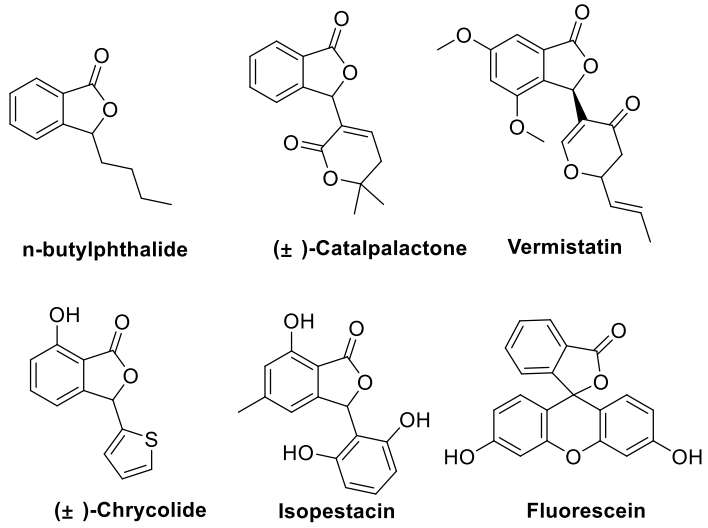
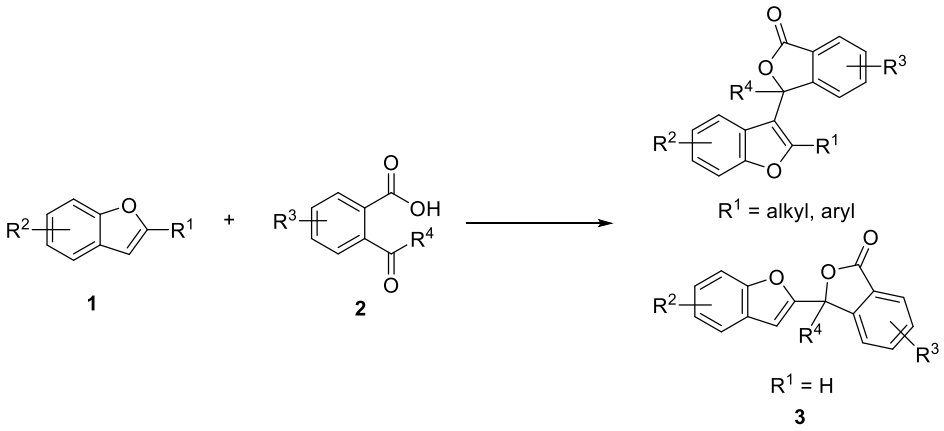


Figure 1. Examples of biologically active 3-substituted phthalides

As such, the construction of 3-substituted phthalides has attracted significant interest over the years.[18, 19] Despite that a variety of synthetic approaches have been developed, the majority of these protocols generally suffer from the requirement of excess amounts of substrates, harsh conditions, and/or use of expensive or toxic transition-metal catalysts.[5, 20] Of the various strategies, Friedel–Crafts/ lactonization of 2-formylbenzoates and nucleophiles is probably the most easily conceivable mode for formation of 3-substituted phthalides.[21-25]

On the other hand, the benzofuran core is associated with many commercially available drugs including Dronedarone, Amiodarone, Benzbromarone, Methoxsalen, Fruquintinib.[26, 27] Due to the wide range of biological profiles of benzofurans and 3-substituted phthalides, compounds containing the benzofuran and phthalide moieties can exhibit potential biological activities.

However, the synthesis of these both containing compounds has been scarcely studied, most notably those bearing an 3-benzofuryl-substituted phthalides. Consequently, the development of efficient and straightforward methodologies for the construction of 3-benzofuryl-substituted phthalides are greatly needed. we predicted that benzofurans might serve as potential nucleophiles suitable for use in the Friedel–Crafts/lactonization with phthalaldehydic acid for construction new benzofuran and phthalide-containing biheterocycles. Herein, we present a practical and efficient broad substrate-scope approach for the synthesis 3-benzofuryl-substituted phthalides, with moderate to excellent yields (Scheme 1). Importantly, 2-ketobenzoic acid can be perfomered to generate, and proceeds with high regioselectivity in our approach.



Scheme 1. The synthesis of 3-benzofuryl-substituted phthalides

Results and Discussion

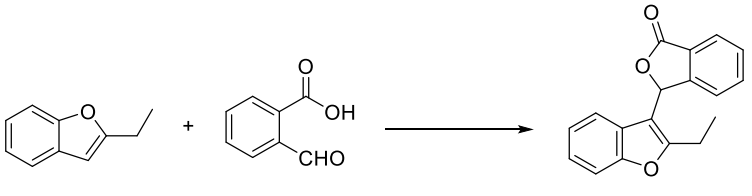
Our investigation started with using 2-ethyl-1-benzofuran (**1a**, 1.0 equiv) and 2-formylbenzoic acid (**2a**, 1.0 equiv) as the model substrates. The experiment was first performed without a mediator in dichloroethane (DCE), while none of the desired product was obtained even at reflux temperature. Employing $AlCl_3$ as the mediator, the reaction can performed even at room temperature using dichloromethane (DCM) as a solvent, furnishing the corresponding products **3a** in 68% yields, establishing the necessity of the metal salt.

Encouraged by this result, we further examined the reactivity with different Lewis acid (entries **3–8**). To our delight, $FeCl_3$ was found as the most efficient mediator, yielding **3a** with 82% yield. Further screening of the solvents indicated DCM was the best choice. Other solvents such as toluene, THF, and 1,4-dioxane were less efficient and delivered the desired compound at a lower yield. When the reaction was conducted in water, there was no detection of any traces of the corresponding phthalide (entry 12).

Next, we examined the effects of different ratios of substrates on the reactivity. Increasing the 2-formylbenzoic acid loading to 1.1 equiv resulted in an increase in the yield of **3a** to 90% (entry 13). There was no change in the yield of the **3a** on increasing the amount of 2-formylbenzoic acid further (entry 14). Thereafter, we found that decreasing the concentration of the mediator led to a drop in the yield of the reaction (entry 15,16).

According to the above optimizations, it was found that 1.0 eq. of $FeCl_3$ and 1.1 eq. of a 2-formylbenzoic acid in DCM are best suited for the reaction, giving a 90% yield of **3a**.

Table 1. Optimization of the reaction conditions[a].



1a **2a** **3a**

Entry	Mediator (eq)	Solvent	**1a/2a** (molar ratio)	yield(%)[b]

1	None	DCE	1	0[c]
2	$AlCl_3$ (1.0)	DCM	1	68
3	$ZnCl_2$ (1.0)	DCM	1	42
4	$FeCl_3$ (1.0)	DCM	1	82
5	$FeBr_3$ (1.0)	DCM	1	70
6	$Fe(OTf)_3$ (1.0)	DCM	1	53
7	$SnCl_4$ (1.0)	DCM	1	32
8	$TiCl_4$ (1.0)	DCM	1	25
9	$FeCl_3$ (1.0)	toluene	1	65
10	$FeCl_3$ (1.0)	THF	1	71
11	$FeCl_3$ (1.0)	1,4-dioxane	1	60
12	$FeCl_3$ (1.0)	H_2O	1	0[c]
13	$FeCl_3$ (1.0)	DCM	1.1	90
14	$FeCl_3$ (1.0)	DCM	1.2	90
15	$FeCl_3$ (0.8)	DCM	1	75
16	$FeCl_3$ (0.5)	DCM	1	48

[a] Reaction conditions: **1a** (1.0 mmol), solvent (2 mL), room temperature, 1 h.

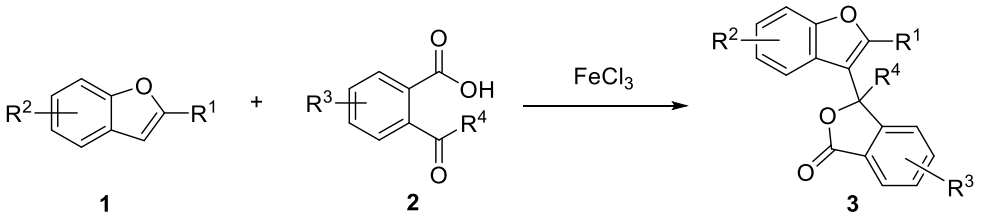
[b] Isolated yield.

[c] The reaction temperature was 70 °C.

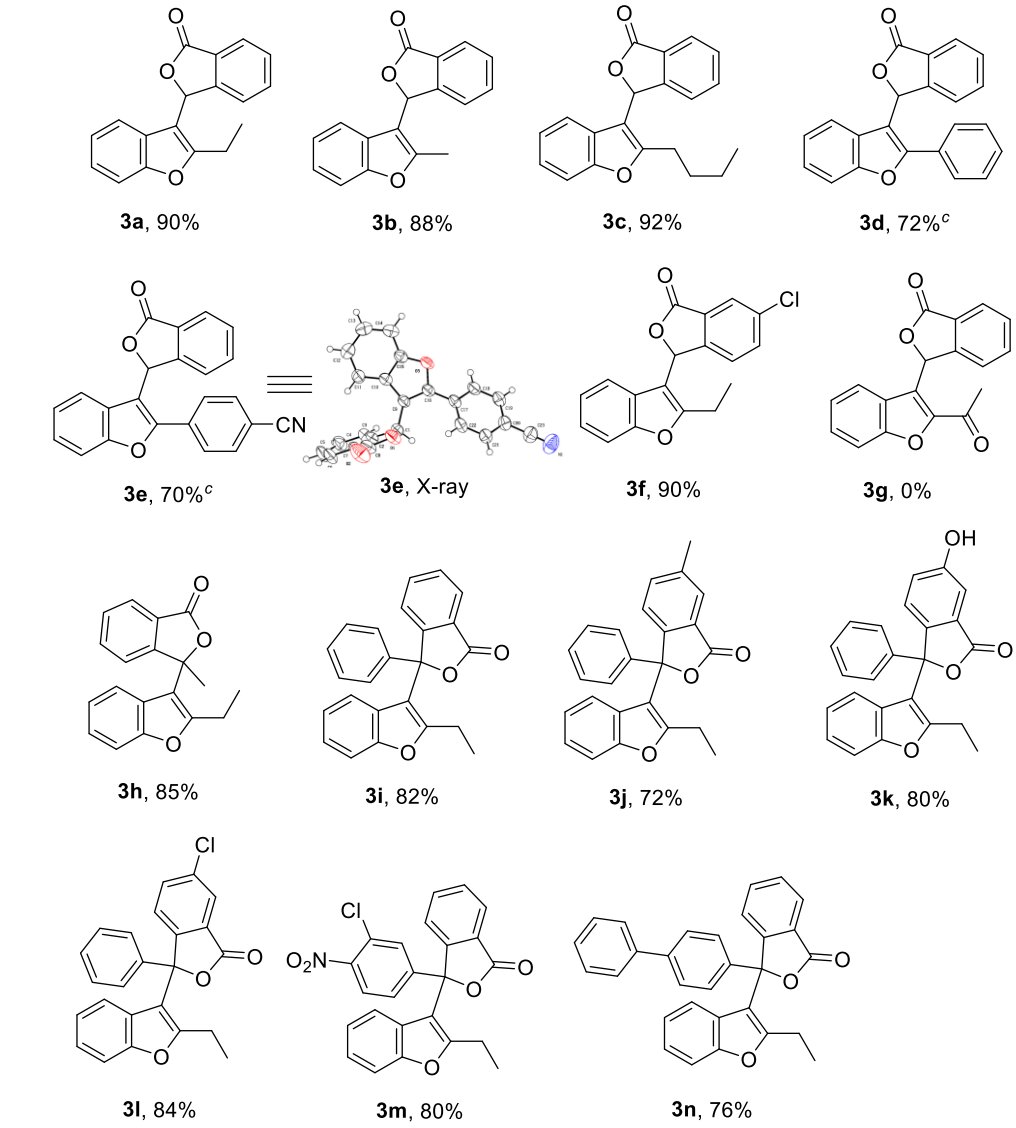
After establishing the optimal conditions for the phthalide synthesis, we proceeded to examine the reaction scope in respect of the benzofurans. The results were illustrated in Table 2. Various 2-substituted benzofurans were examined firstly, and the corresponding products **3b-e** were all obtained in moderate to excellent yields. Delightedly, benzofurans **1d** and **1e** bearing the 2-phenyl-substituted were also amenable to the reaction, formed in moderate yields at reflux condition in DCE. The structure of **3e** was further confirmed by X-ray crystallographic study. For 5-chloro-2-formylbenzoic acid, its corresponding product **3f** was obtained in 90% yield, comparable to that of compound **3a**. While no product was detected when 2-acetylbenzofuran was used, suggesting that strongly electron-withdrawing groups are not suitable for this protocol.

After the successful synthesis of phthalide synthesis, it motivated us to extend the scope from the 2-formylbenzoic acid to 2-ketobenzoic acid core, which may be more challenging, and are barely reported. Therefore, a series of 2-ketobenzoic acid were investigated. Encouragingly, acetylbenzoic acid could reacted smoothly with 2-ethyl-1-benzofuran (**2a**) to afford the desired **3h** in excellent yields. Thereafter, various substituted 2-ketobenzoic acid bearing electron-donating or electron-withdrawing groups could also preferentially be applied to this established method, affording the corresponding products **3i–n** in moderate to good yields, illustrating the generality of our current methodology.

Table 2. Substrate scope for 3-benzofuryl-substituted phthalides [a,b]



1 **2** **3**



[a] Reaction conditions: benzofuran**1** (1.0 mmol), phthalaldehydic acid **2** (1.1 mmol), $FeCl_3$ (1.0 mmol), DCM (2 mL), rt, 1 h.

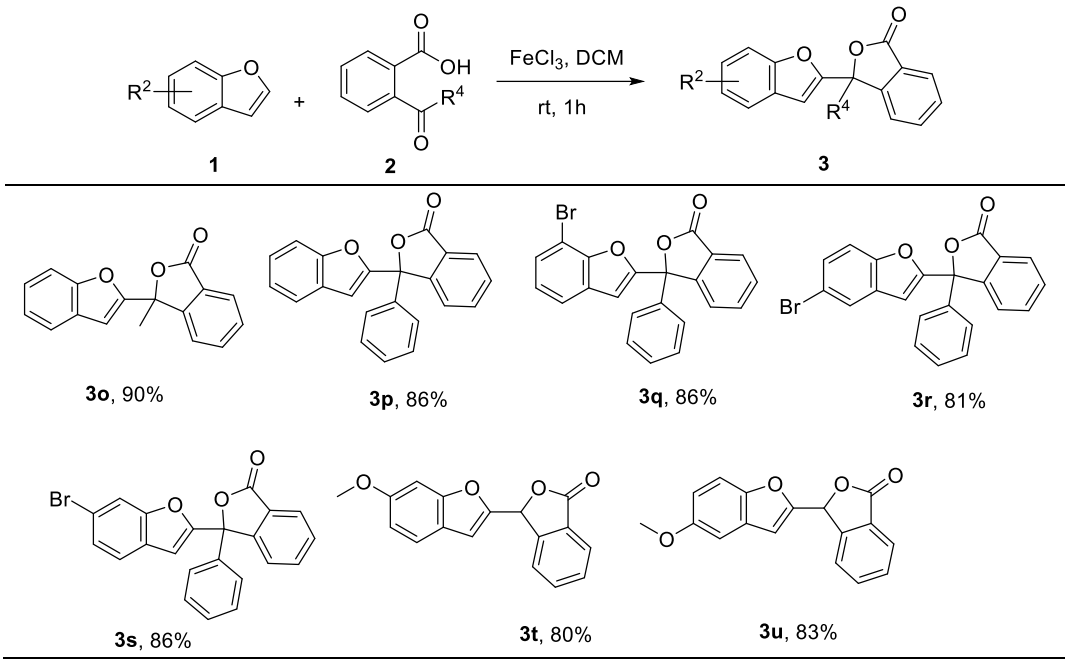
[b] Isolated yields are shown.

[c] reflux in DCE.

At last, we explored regioselectivity of the benzofuran in C-2 and C-3 in this protocol. To our exiting, various 2-ketobenzoic acid and different substituted benzofuran all smoothly participated in this process, affording the desired products in good yields (**3o-3u**). It is worth noting that only 3-(2'- benzofuryl)-phthalides were afforded exclusively under the optimal conditions, and the 3-(3'-benzofuryl)-phthalides were not observed in these reactions, illustrating the high regioselectivity. We suppose ketone substrates are more regioselective than aldehyde substrates because ketones are significantly less reactive than aldehydes. In addition, the C2-position of benzofuran should be a little more reactive than the C3-position due to the oxygen atom having relatively strong electronegativity.

Further experimental research indicated that electron-rich substituted benzofurans proceeds with complete C-2 regioselectivity in this transformation. Such as 5-methoxybenzofuran and 6-methoxybenzofuran could also be used as the qualified substrates (**3t** and **3u**), the products could be isolated in 80%, and 88% yield, respectively.

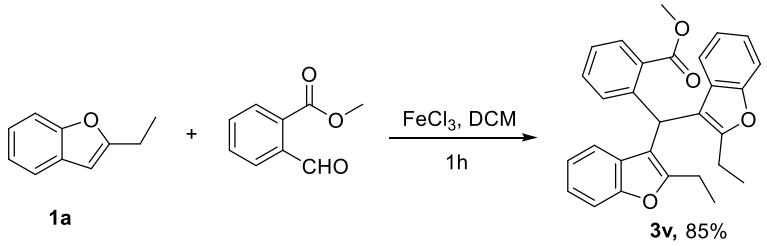
Table 3. Substrate scope for 2-substituted benzofurans [a,b]



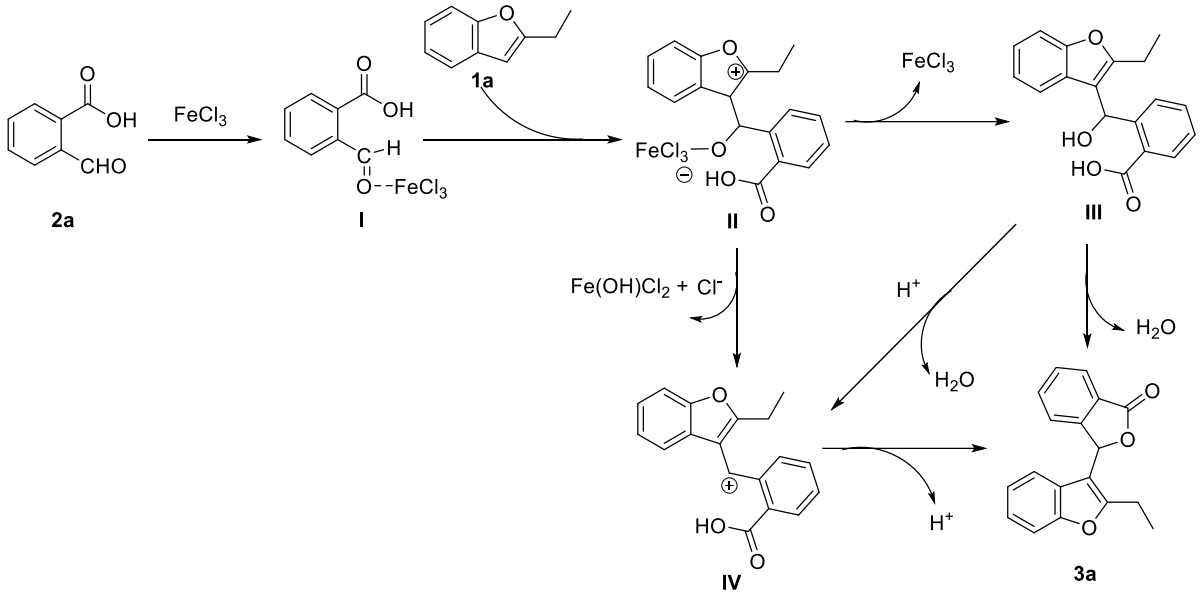
[a] Reaction conditions: benzofuran **1** (1.0 mmol), phthalaldehydic acid **2** (1.1 mmol), $FeCl_3$ (1.0 mmol), DCM (2 mL), rt, 1 h.

[b] Isolated yields are shown.

For elucidation of the reaction mechanism, a control experiment between 2-ethyl-1-benzofuran (**1a)** and methyl 2-formylbenzoate was carried out (Scheme 2). While the corresponding product was not detected, instead, the bis(benzofuryl)phthalide was obtained in high yeild (85%). Based on these results and also the literature precedents[23, 28-31], we proposed that product **3a** can be formed in two paths, and a plausible reaction pathway was proposed and depicted in Scheme 3. First, the Friedel–Crafts reaction of phthalaldehydic acid (**2a)** with 2-ethyl-1-benzofuran (**1a)** generates the intermediate **II** in the presence of $FeCl_3$. At this time, in one way, intermediate **II** can undergo a rearomatization to yield benzyl alcohol **III,** which is followed by intramolecular cyclization to form the final product **3a** quickly. In the other way, complex **II** undergoes a cleavage of the C–O bond providing the benzylic carbocation **IV**. In addition, **III** also can be activated by HCl and undergoes an elimination to afford the carbocation **IV**. At last, the resulting carbocation reacts with the acid group to produce the product **3a**. As for bisbenzofuryl product **3v**, the benzyl alcohol intermediate undergoes second Friedel–Crafts reaction with another equivalent of **1a,** instead of intramolecular cyclization.



Scheme 2. Control experiment



Scheme 3. A plausible mechanism for the formation of **3a**

Conclusions

In conclusion, we have proposed a simple and effective procedure for straightforward construction 3-benzofuryl-substituted phthalides via cyclization reactions of benzofurans with 2-carbonyl-benzoic acid. The broad substrate scope, high regioselective, and high atom economy of this method make it an attractive alternative for the synthesis of complex biheterocycles, which may provide a promising approach for synthesis of bioactive compounds.

Experimental Section

General Information.

All the reagents and solvents were obtained via commercial sources and used without further purification. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F254 plates (Qingdao Ocean Chemical Company, China). Column chromatography was carried out on silica gel (200-300 mesh, Qingdao Ocean Chemical Company, China). ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker 600 MHz and 151 MHz respectively. Chemical shift values are reported in ppm with reference to solvent signals, ^{1}H NMR (7.26 ppm) and ^{13}C NMR (77.00 ppm). Data are reported in chemical shifts, integration, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplets, dd = doublet of doublet), and coupling constants (*J*) in Hz. HRMS spectrometry data were collected on an electrospray ionization (ESI) produced by a AB SCIEX X500R QTOF.

The typical reaction procedures

A 10 mL dried round-bottom flask was charged with benzofurans (1 mmol, 1.0 equiv) and 2-carbonyl-benzoic acid 2 (1.1 mmol, 1.1 equiv), DCM or DCE (2 mL) was added, and the solution was stirred at room temperature or 70^{o}C. Subsequently, ferric trichloride ($FeCl_3$) (1 mmol, 1 equiv) was added quickly. Upon complete addition, the reaction flask was stirred at room temperature for 1 h, and monitored by TLC. Then the reaction was quenched with H_2O (1 mL), and washed with 1N HCl (3 × 2 mL). The organic phase was dried over Na_2SO_4.

After evaporation of the solvents, the residue was purified by flash column chromatography (silica gel, PE–EtOAc, 10: 1 to afford the desired products **3**. The ^{1}H NMR and ^{13}C NMR spectra of the isolated ammonium salts were recorded in $CDCl_3$.

Characterization data for the compounds

3-(2-ethylbenzofuran-3-yl)isobenzofuran-1(3H)-one (3a). White solid (249.8 mg, 90%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (d, *J* 7.5 Hz, 1H), 7.66 (t, *J* 7.4 Hz, 1H), 7.62 (t, *J* 7.4 Hz, 1H), 7.40 (d, *J* 8.3 Hz, 1H), 7.33 (d, *J* 7.4 Hz, 1H), 7.16 (t, *J* 7.8 Hz, 1H), 6.95 (t, *J* 7.6 Hz, 1H), 6.64 (s, 1H), 6.46 (d, *J* 7.8 Hz, 1H), 2.91 (q, *J* 7.5 Hz, 2H), 1.40 (t, *J* 7.6 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.33, 160.42, 154.13, 148.53, 134.46, 129.70, 126.39, 126.22, 125.76, 123.95, 122.90, 122.81, 119.13, 111.10, 109.10, 75.76, 20.23, 13.21. HRMS (ESI) calcd for $C_{18}H_{14}O_3$: $[M + H]^+$ = 279.1016, found *m/z* = 279.1008.

3-(2-methylbenzofuran-3-yl)isobenzofuran-1(3H)-one (3b). White solid (233.0 mg, 88%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (d, *J* 7.5 Hz, 1H), 7.66 (t, *J* 7.3 Hz, 1H), 7.62 (t, *J* 7.4 Hz, 1H), 7.39 (d, *J* 8.2 Hz, 1H), 7.34 (d, *J* 7.5 Hz, 1H), 7.16 (t, *J* 7.7 Hz, 1H), 6.96 (t, *J* 7.5 Hz, 1H), 6.62 (s, 1H), 6.48 (d, *J* 7.8 Hz, 1H), 2.56 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.29, 155.39, 154.10, 148.46, 134.48, 129.71, 126.38, 126.26, 125.77, 123.95, 122.94, 122.85, 118.95, 111.00, 110.10, 75.82, 12.50. HRMS (ESI) calcd for $C_{17}H_{12}O_3$: $[M + H]^+$ = 265.0859, found *m/z* = 265.0850.

3-(2-butylbenzofuran-3-yl)isobenzofuran-1(3H)-one (3c). White solid (280.7 mg, 92%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (d, *J* 7.5 Hz, 1H), 7.66 (t, *J* 7.1 Hz, 1H), 7.62 (t, *J* 7.4 Hz, 1H), 7.40 (d, *J* 8.2 Hz, 1H), 7.32 (d, *J* 7.4 Hz, 1H), 7.16 (t, *J* 7.7 Hz, 1H), 6.94 (t, *J* 7.6 Hz, 1H), 6.62 (s, 1H), 6.43 (d, *J* 7.8 Hz, 1H), 2.89 (t, *J* 7.5 Hz, 1H), 1.85 – 1.75 (m, 1H), 1.50 – 1.39 (m, 1H), 0.97 (t, *J* 7.4 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.33, 159.50, 154.15, 148.56, 134.46, 129.69, 126.46, 126.18, 125.75, 123.92, 122.92, 122.79, 119.08, 111.08, 109.78, 75.81, 30.66, 26.44, 22.34, 13.79. HRMS (ESI) calcd for $C_{20}H_{18}O_3$: $[M + H]^+$ = 307.1329, found *m/z* = 307.1319.

3-(2-phenylbenzofuran-3-yl)isobenzofuran-1(3H)-one (3d). White solid (234.8 mg, 72%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12 – 8.06 (m, 1H), 7.92 (d, *J* 7.3 Hz, 2H), 7.66 – 7.63 (m, 2H), 7.57 (t, *J* 7.5 Hz, 2H), 7.54 – 7.48 (m, 2H), 7.37 – 7.30 (m, 1H), 7.23 (t, *J* 7.7 Hz, 1H), 6.94 (t, *J* 7.6 Hz, 1H), 6.81 (s, 1H), 6.26 (d, *J* 7.9 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.33, 156.91, 154.39, 148.19, 134.47, 129.91, 129.83, 129.36, 129.12, 128.38, 126.53, 126.51, 125.87, 124.88, 123.27, 123.10, 120.10, 111.55, 110.21, 76.38. HRMS (ESI) calcd for $C_{22}H_{14}O_3$: $[M + H]^+$ = 327.1016, found *m/z* = 327.1014.

4-(3-(3-oxo-1,3-dihydroisobenzofuran-1-yl)benzofuran-2-yl)benzonitrile (3e). White solid (254.8 mg, 70%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14 – 8.08 (m, 1H), 8.05 (d, *J* 8.3 Hz, 2H), 7.84 (d, *J* 8.3 Hz, 2H), 7.74 – 7.64 (m, 2H), 7.54 (d, *J* 8.3 Hz, 1H), 7.39 – 7.32 (m, 1H), 7.29 (t, *J* 7.7 Hz, 1H), 6.98 (t, *J* 7.6 Hz, 1H), 6.77 (s, 1H), 6.26 (d, *J* 7.9 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.94, 154.64, 154.27, 147.57, 134.63, 133.55, 132.81, 130.14, 128.63, 126.41, 126.19, 126.09, 125.90, 123.55, 123.25, 120.54, 118.29, 113.22, 112.61, 111.78, 75.55. HRMS (ESI) calcd for $C_{23}H_{13}NO_3$: $[M + H]^+$ = 352.0968, found *m/z* = 352.0966.

6-chloro-3-(2-ethylbenzofuran-3-yl)isobenzofuran-1(3H)-one (3f). White solid (281.4 mg, 90%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.62 (d, *J* 8.1 Hz, 1H), 7.41 (d, *J* 8.3 Hz, 1H), 7.26 (d, *J* 9.0 Hz, 1H), 7.22 – 7.15 (m, 1H), 6.98 (t, *J* 7.5 Hz, 1H), 6.61 (s, 1H), 6.47 (d, *J* 7.8 Hz, 1H), 2.91 (q, *J* 7.6 Hz, 2H), 1.40 (t, *J* 7.6 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.80, 160.63, 154.14, 146.67, 136.07, 134.78, 128.23, 125.97, 125.69, 124.22, 124.11, 122.97, 118.97, 111.22, 108.52, 75.69, 20.23, 13.25. HRMS (ESI) calcd for $C_{18}H_{13}ClO_3$: $[M + H]^+$ = 313.0631, found *m/z* = 313.0629.

3-(2-ethylbenzofuran-3-yl)-3-methylisobenzofuran-1(3H)-one (3h). White solid (248.5 mg, 85%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (d, *J* 7.6 Hz, 1H), 7.63 (t, *J* 7.2 Hz, 1H), 7.54 (t, *J* 7.5 Hz, 1H), 7.51 (d, *J* 7.7 Hz, 1H), 7.39 (d, *J* 8.2 Hz, 1H), 7.32 (d, *J* 7.9 Hz, 1H), 7.21 (t, *J* 7.7 Hz, 1H), 7.14 (t, *J* 7.6 Hz, 1H), 2.85 – 2.74 (m, 2H), 2.21 (s, 3H),

1.23 (t, *J* 7.5 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.76, 157.35, 154.35, 153.81, 134.49, 129.42, 127.02, 125.86, 125.08, 123.71, 122.68, 121.92, 120.47, 113.30, 111.12, 85.36, 28.00, 21.94, 13.03. HRMS (ESI) calcd for $C_{19}H_{16}O_3$: $[M + H]^+$ = 293.1172, found *m/z* = 293.1167.

3-(2-ethylbenzofuran-3-yl)-3-phenylisobenzofuran-1(3H)-one (3i). White solid (290.6 mg, 82%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (d, *J* 7.6 Hz, 1H), 7.67 (t, *J* 7.5 Hz, 1H), 7.64 – 7.56 (m, 2H), 7.51 – 7.45 (m, 2H), 7.42 – 7.32 (m, 4H), 7.16 (t, *J* 7.7 Hz, 1H), 6.95 (t, *J* 7.6 Hz, 1H), 6.52 (d, *J* 8.0 Hz, 1H), 2.44 – 2.29 (m, 2H), 1.09 (t, *J* 7.5 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.68, 159.07, 153.79, 151.94, 140.21, 134.22, 129.73, 128.94, 128.81, 127.46, 126.53, 126.10, 125.50, 124.00, 123.64, 122.52, 120.87, 113.86, 110.88, 88.38, 21.48, 12.59. HRMS (ESI) calcd for $C_{24}H_{18}O_3$: $[M + H]^+$ = 355.1329, found *m/z* = 355.1321.

3-(2-ethylbenzofuran-3-yl)-6-methyl-3-phenylisobenzofuran-1(3H)-one (3j). White solid (265.3 mg, 72%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97 (d, *J* 7.6 Hz, 1H), 7.65 (t, *J* 7.4 Hz, 1H), 7.62 – 7.55 (m, 2H), 7.38 (d, *J* 8.2 Hz, 1H), 7.34 (d, *J* 8.0 Hz, 2H), 7.16 (t, *J* 7.2 Hz, 3H), 6.96 (t, *J* 7.6 Hz, 1H), 2.44 – 2.36 (m, 2H), 2.35 (s, 3H), 1.10 (t, *J* 7.5 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.75, 158.94, 153.78, 152.16, 138.87, 137.15, 134.17, 129.61, 129.46, 127.51, 126.51, 126.03, 125.50, 123.91, 123.58, 122.47, 120.95, 113.93, 110.84, 88.45, 21.50, 21.17, 12.62. HRMS (ESI) calcd for $C_{25}H_{20}O_3$: $[M + H]^+$ = 368.1485, found *m/z* = 368.1484.

3-(2-ethylbenzofuran-3-yl)-6-hydroxy-3-phenylisobenzofuran-1(3H)-one (3k). White solid (296.0 mg, 80%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97 (d, *J* 7.8 Hz, 1H), 7.66 (t, *J* 7.4 Hz, 1H), 7.61 – 7.54 (m, 2H), 7.37 (d, *J* 8.2 Hz, 1H), 7.24 (d, *J* 8.5 Hz, 2H), 7.15 (t, *J* 7.7 Hz, 1H), 6.96 (t, *J* 7.6 Hz, 1H), 6.81 (d, *J* 8.2 Hz, 2H), 6.63 (d, *J* 7.9 Hz, 1H), 2.50 – 2.36 (m, 2H), 1.09 (t, *J* 7.5 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.46, 158.68, 156.64, 153.78, 152.26, 134.41, 129.64, 128.40, 127.35, 126.02, 125.39, 123.85, 123.65, 122.55 , 120.93, 115.69, 113.91, 110.88, 89.04, 21.51, 12.67. HRMS (ESI) calcd for $C_{24}H_{18}O_4$: $[M + H]^+$ = 371.1278, found *m/z* = 371.1263.

6-chloro-3-(2-ethylbenzofuran-3-yl)-3-phenylisobenzofuran-1(3H)-one (3l). White solid (326.6 mg, 84%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (d, *J* 7.6 Hz, 1H), 7.68 (t, *J* 7.5 Hz, 1H), 7.61 (t, *J* 7.5 Hz, 1H), 7.58 (t, *J* 7.9 Hz, 1H), 7.40 (t, *J* 8.2 Hz, 3H), 7.34 (d, *J* 8.5 Hz, 2H), 7.18 (t, *J* 7.7 Hz, 1H), 6.98 (t, *J* 7.6 Hz, 1H), 6.55 (d, *J* 7.9 Hz, 1H), 2.46 – 2.33 (m, 2H), 1.11 (t, *J* 7.5 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.39, 159.02, 153.80, 151.53, 138.83, 135.04, 134.38, 129.94, 129.05, 128.01, 127.22, 126.25, 125.37, 123.80, 122.65, 120.76, 113.42, 110.98, 87.78, 21.56, 12.59. HRMS (ESI) calcd for $C_{24}H_{17}ClO_3$: $[M + H]^+$ = 389.0939, found *m/z* = 389.0931.

3-(3-chloro-4-nitrophenyl)-3-(2-ethylbenzofuran-3-yl)isobenzofuran-1(3H)-one (3m). White solid (336.6 mg, 80%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03 (d, *J* 7.6 Hz, 1H), 7.94 (d, *J* 2.2 Hz, 1H), 7.74 (t, *J* 8.0 Hz, 1H), 7.70 – 7.64 (m, 2H), 7.59 (d, *J* 7.7 Hz, 1H), 7.57 (d, *J* 8.5 Hz, 1H), 7.42 (d, *J* 8.2 Hz, 1H), 7.21 (t, *J* 7.8 Hz, 1H), 7.02 (t, *J* 7.6 Hz, 1H), 6.52 (d, *J* 7.9 Hz, 1H), 2.47 – 2.36 (m, 2H), 1.13 (t, *J* 7.5 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.69, 159.29, 153.86, 150.33, 148.07, 141.07, 134.88, 132.54, 131.18, 130.55, 127.79, 126.69, 126.67, 125.20, 124.18, 123.65, 123.48, 122.98, 120.35, 112.46, 111.28, 86.62, 21.69, 12.53. HRMS (ESI) calcd for $C_{24}H_{16}ClNO_5$: $[M + H]^+$ = 434.0790, found *m/z* = 434.0790.

3-([1,1'-biphenyl]-4-yl)-3-(2-ethylbenzofuran-3-yl)isobenzofuran-1(3H)-one (3n). White solid (327.1mg, 76%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (d, *J* 7.6 Hz, 1H), 7.69 (t, *J* 7.4 Hz, 1H), 7.64 (d, *J* 7.6 Hz, 1H), 7.62 – 7.56 (m, 5H), 7.54 (d, *J* 8.4 Hz, 2H), 7.43 (t, *J* 7.6 Hz, 2H), 7.40 (d, *J* 8.2 Hz, 1H), 7.35 (t, *J* 7.4 Hz, 1H), 7.17 (t, *J* 7.7 Hz, 1H), 6.97 (t, *J* 7.6 Hz, 1H), 6.60 (d, *J* 7.9 Hz, 1H), 2.49 – 2.35 (m, 2H), 1.12 (t, *J* 7.5 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.67, 159.09 153.81 151.94, 141.74, 140.08, 139.10, 134.29, 129.77, 128.89, 127.74, 127.43, 127.10, 127.02, 126.15, 125.51, 123.98, 123.68, 122.57, 120.94, 113.78, 110.91, 88.29, 21.56, 12.62. HRMS (ESI) calcd for $C_{30}H_{22}O_3$: $[M + H]^+$ = 431.1642, found *m/z* = 431.1637.

3-(benzofuran-2-yl)-3-methylisobenzofuran-1(3H)-one (3o). White solid (237.7 mg, 90%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (d, *J* 7.6 Hz, 1H), 7.70 (t, *J* 7.5 Hz, 1H), 7.58 (dd, *J* 13.6, 7.5 Hz, 2H), 7.52 (d, *J* 7.7 Hz, 1H), 7.42 (d, *J* 8.3 Hz, 1H), 7.28 (t, *J* 7.2 Hz, 1H), 7.21 (t, *J* 7.4 Hz, 1H), 6.68 (s, 1H), 2.10 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ

169.35, 155.26, 154.93, 151.31, 134.47, 129.78, 127.54, 126.01, 125.44, 125.00, 123.15, 122.20, 121.43 , 111.49, 104.14, 83.20, 24.92. HRMS (ESI) calcd for $C_{17}H_{12}O_3$: $[M + H]^+$ = 265.0859, found *m/z* = 265.0861.

3-(benzofuran-2-yl)-3-phenylisobenzofuran-1(3H)-one (3p). White solid (280.6 mg, 86%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.98 (d, *J* 7.7 Hz, 1H), 7.78 – 7.70 (m, 2H), 7.61 (t, *J* 6.9 Hz, 1H), 7.53 (d, *J* 7.7 Hz, 1H), 7.49 – 7.44 (m, 2H), 7.42 (d, *J* 8.3 Hz, 1H), 7.40 – 7.35 (m, 3H), 7.29 (t, *J* 7.6 Hz, 1H), 7.22 (t, *J* 7.4 Hz, 1H), 6.74 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.27, 155.58, 154.49, 149.93, 137.84, 134.48, 129.98, 129.20, 128.76, 127.34, 126.57, 126.14, 125.49, 125.14, 124.04, 123.24, 121.53, 111.65, 106.65 , 86.76. HRMS (ESI) calcd for $C_{22}H_{14}O_3$: $[M + H]^+$ = 327.1021, found *m/z* = 327.1023.

3-(7-bromobenzofuran-2-yl)-3-phenylisobenzofuran-1(3H)-one (3q). White solid (348.3 mg, 86%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97 (d, *J* 7.7 Hz, 1H), 7.85 (d, *J* 7.8 Hz, 1H), 7.76 (t, *J* 7.9 Hz, 1H), 7.61 (t, *J* 7.4 Hz, 1H), 7.47 (d, *J* 7.7 Hz, 1H), 7.46 – 7.41 (m, 3H), 7.40 – 7.36 (m, 3H), 7.10 (t, *J* 7.8 Hz, 1H), 6.89 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.16, 155.35, 152.70, 149.71, 137.68, 134.66, 130.10, 129.33, 128.81, 128.66, 128.11, 126.63, 126.12, 125.32, 124.55, 124.31, 120.67, 106.54, 104.23, 86.50, 26.93. HRMS (ESI) calcd for $C_{22}H_{13}BrO_3$: $[M + H]^+$ = 405.0121, found *m/z* = 405.1118.

3-(5-bromobenzofuran-2-yl)-3-phenylisobenzofuran-1(3H)-one (3r). White solid (328.2mg, 81%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.98 (d, *J* 7.7 Hz, 1H), 7.77 – 7.71 (m, 2H), 7.66 (s, 1H), 7.64 – 7.60 (m, 1H), 7.47 – 7.41 (m, 2H), 7.41 – 7.36 (m, 4H), 7.28 (d, *J* 8.8 Hz, 1H), 6.69 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.07, 155.95, 154.30, 149.57, 137.53, 134.59, 130.14, 129.33 , 128.84, 128.12, 126.50, 126.24, 125.44, 124.17, 123.99, 116.31, 113.12, 106.00, 86.45. HRMS (ESI) calcd for $C_{22}H_{13}BrO_3$: $[M + H]^+$ =405.0121, found *m/z* = 405.1119.

3-(6-bromobenzofuran-2-yl)-3-phenylisobenzofuran-1(3H)-one (3s). White solid (348.1 mg,86%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.98 (d, *J* 7.7 Hz, 1H), 7.76 – 7.72 (m, 2H), 7.62 (t, *J* 6.8 Hz, 1H), 7.59 (s, 1H), 7.47 – 7.41 (m, 2H), 7.41 – 7.32 (m, 5H), 6.72 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.10, 155.78, 155.27, 149.62, 137.53, 134.57, 130.12, 129.33, 128.82, 126.76, 126.52, 126.39, 126.22, 125.44, 123.98, 122.46, 118.42, 115.13, 106.44, 86.49. HRMS (ESI) calcd for $C_{22}H_{13}BrO_3$: $[M + H]^+$ = 405.0121, found *m/z* = 405.1122.

(6-methoxybenzofuran-2-yl)isobenzofuran-1(3H)-one (3t). White solid (224.4 mg, 80%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 – 7.93 (m, 1H), 7.84 – 7.70 (m, 2H), 7.68 – 7.59 (m, 2H), 7.41 (d, *J* 8.6 Hz, 1H), 6.97 (s, 1H), 6.91 – 6.86 (m, 1H), 6.78 (s, 1H), 3.82 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.09, 158.73, 156.60, 150.86, 144.10, 112.72, 106.90, 99.06, 95.93, 82.28, 55.69. HRMS (ESI) calcd for $C_{17}H_{12}O_4$: $[M + H]^+$ = 281.0808, found *m/z* = 281.0813.

3-(5-methoxybenzofuran-2-yl)isobenzofuran-1(3H)-one (3u). White solid (232.5 mg, 83%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (d, *J* 7.6 Hz, 1H), 7.60 (t, *J* 7.5 Hz, 1H), 7.54 (t, *J* 7.5 Hz, 1H), 7.46 (s, 1H), 7.45 (d, *J* 6.7 Hz, 1H), 7.38 (d, *J* 7.6 Hz, 1H), 7.16 (s, 1H), 7.00 (d, *J* 9.0 Hz, 1H), 6.18 (s, 1H), 3.94 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.11, 150.38, 150.30, 146.58, 134.30, 129.15, 126.16, 125.90, 125.43, 122.94, 115.88, 112.35, 109.12, 105.14, 57.12. HRMS (ESI) calcd for $C_{17}H_{12}O_4$: $[M + H]^+$ = 281.0808, found *m/z* = 281.0810.

methyl 2-(bis(2-ethylbenzofuran-3-yl)methyl)benzoate (3v). White solid (186.4 mg, 85%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (d, *J* 7.4 Hz, 1H), 7.41 – 7.32 (m, 5H), 7.13 (t, *J* 7.7 Hz, 2H), 6.96 (t, *J* 7.3 Hz, 2H), 6.86 (d, *J* 9.0 Hz, 3H), 3.57 (s, 3H), 2.54 – 2.42 (m, 4H), 1.09 (t, *J* 7.5 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.18, 167.49, 156.87, 153.80, 142.34, 131.59, 130.83, 130.72, 129.73, 129.47, 126.91, 123.04, 122.20, 119.83, 114.25, 110.61, 51.97, 34.09, 20.24, 12.16. HRMS (ESI) calcd for $C_{29}H_{26}O_4$: $[M - H]^-$ = 437.1747, found *m/z* = 437.1764.

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Supplementary Material

Characterization data including copies of ^{1}H and ^{13}C NMR spectra associated with this paper and X-ray crystallography data for compound **3e** can be found in the online version.

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