

Facile and eco-friendly synthesis of bis(2-tetrahydrobenzofuranyl)alkanes catalyzed by $\text{H}_2\text{SO}_4 \cdot \text{SiO}_2$ under solvent-free conditions

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Abstract

A series of bis(2-tetrahydrobenzofuranyl)alkanes were efficiently prepared in high yields (69-98%) from 3-methyl-6,7-dihydrobenzofuran-4(5*H*)-ones and aldehydes under solvent-free conditions. The eco-friendly condensation reaction was smoothly catalyzed by $\text{H}_2\text{SO}_4 \cdot \text{SiO}_2$ (30% w/w) in three minutes at 90 °C, and the catalyst could also be recycled up to nine successive cycles without significant loss in catalytic activity.

Keywords: Bis(2-tetrahydrobenzofuranyl)alkanes, $\text{H}_2\text{SO}_4 \cdot \text{SiO}_2$, condensation reaction, solvent free condition

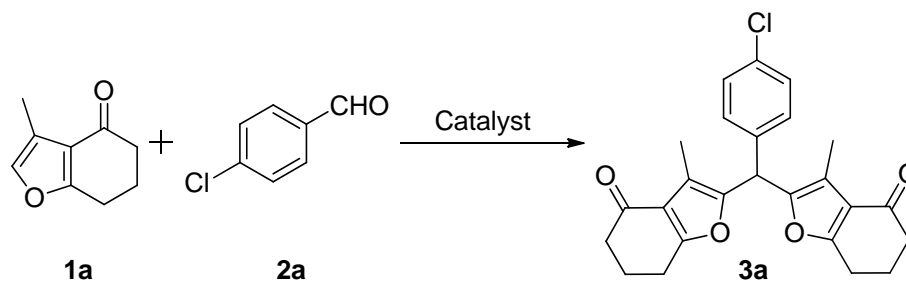
Introduction

Tetrahydrobenzofuran derivatives are important heterocycles in natural products,¹ pharmaceuticals² and diverse synthetic intermediates³ because of their various pharmacological activities including antioxidant,⁴ antitumor,⁵ anti-ulcer,⁶ photoreagents² and so on. The bioactive bis(heterocyclyl)alkanes constitute valuable building blocks used as protective groups,⁷ photochromic materials⁸ and drugs⁹ in synthetic, industrial and medicinal chemistry. However, the available methods for the synthesis of these bis(heterocyclyl)alkanes were often limited to small-scale reactions owing to expensive substrates,^{10,11} multi-step processes,^{12,13} harsh reaction conditions¹⁴ or low yields.¹⁵ The condensation of heteroaryl species with carbonyl compounds can be promoted under strongly acid conditions.^{10,11} A variety of Lewis acids [e.g., ZnCl_2 ,¹⁶ RuCl_3 ,¹⁷ $\text{Cu}(\text{OTf})_2$,¹⁸ AuCl_3 ,¹⁹ FeCl_3 ²⁰ and $\text{Bi}(\text{OTf})_3$ ¹⁵] are effective catalysts under prolonged refluxing conditions. As a consequence, the need to develop mild and efficient methods for the synthesis of symmetric bis(2-tetrahydrobenzofuranyl)alkanes is still an important and challenging goal.

In recent years, solvent-free organic reactions have gained particular attention owing to their eco-friendly, economic advantages and high yields.^{21,22} As a silica-supported reagent, $\text{H}_2\text{SO}_4 \cdot \text{SiO}_2$ has attracted much attention for its ease of preparation, low cost, high efficiency and environmental benignness.²³ $\text{H}_2\text{SO}_4 \cdot \text{SiO}_2$ has already been used in cycloadditions,²⁴ Beckmann rearrangements,²⁵ glycosylations,²⁶ condensations²⁷ and esterifications.²⁸ During our on-going efforts to develop convenient approaches to tetrahydrobenzofuran derivatives as H^+/K^+ -ATPase inhibitors,²⁹ we discovered that $\text{H}_2\text{SO}_4 \cdot \text{SiO}_2$ was a high-efficient and recyclable catalyst for preparing the bis(2-tetrahydrobenzofuranyl)alkanes in a synthetically practical procedure (solvent-free, stoichiometric ratios and short reaction times) with widely functional group compatibility.

Results and Discussion

As part of our studies on the development of efficient and facile methods for the preparation of bis(2-tetrahydrobenzofuranyl)alkanes **3**, various catalysts, reaction times and temperatures were screened. Initially, 3-methyl-6,7-dihydrobenzofuran-4(5*H*)-one (**1a**)³⁰ and 4-chlorobenzaldehyde (**2a**) were selected as model substrates for the condensation reaction catalyzed by different catalyst according to literature conditions (Scheme 1).



Scheme 1. The model reaction for the synthesis of **3a**.

As shown in Table 1, the use of Brønsted acids at *ca.* 35 °C for 1 or 18 h led to the formation of the product **3a** in moderate yield (entries 1 and 2), whereas the use of Lewis acids exhibited poor catalytic abilities in different solvents (entries 3 and 4). Under solvent-free conditions, the use of copper (II) triflate at *ca.* 35 °C for 12 h gave the product **3a** in 55% isolated yield (entry 5), while the use of $\text{H}_2\text{SO}_4 \cdot \text{SiO}_2$ as catalyst surprisingly gave the product **3a** in an almost theoretical yield (98%) in only 10 min (entry 6). Therefore, $\text{H}_2\text{SO}_4 \cdot \text{SiO}_2$ was chosen as the most efficient catalyst for the condensation of 3-methyl-6,7-dihydrobenzofuran-4(5*H*)-ones and aldehydes under solvent-free conditions.

Table 1. Catalyst screening for the model reaction

Entry	Catalyst (amount)	Solvent	Time (h)	Temp. (°C)	Yield 3a (%) ^a
1	conc. HCl ¹⁰	H ₂ O	1	35	57
2	CF ₃ CO ₂ H (3 equiv.) ¹¹	Solvent-free	18	35	68
3	ZnCl ₂ (150 mol%) ¹⁶	CH ₂ Cl ₂	2	35	25
4	RuCl ₃ •3H ₂ O (10 mol%) ¹⁷	Benzene	36	80	5
5	Cu(OTf) ₂ (10 mol%) ¹⁸	Solvent-free	12	35	55
6	H ₂ SO ₄ •SiO ₂ (30% w/w) ^b	Solvent-free	0.17	45	98

^a Isolated yield of **3a**. ^b Reaction conditions: 3-Methyl-6,7-dihydrobenzofuran-4(5*H*)-one (**1a**, 1.0 mmol), 4-chlorobenzaldehyde (**2a**, 0.5 mmol) and H₂SO₄•SiO₂ (30% weight ratio to **1a**) were mixed and stirred for 10 min at 45 °C.

Encouraged by the solvent-free reaction results, the proper catalytic dosage was also examined (Table 2). When the reaction proceeded for 5 min at 45 °C in the presence of H₂SO₄•SiO₂, the yield of the target **3a** increased as the dosage of the catalyst increased in the range of 8-50% weight ratio to **1a** (entries 2-8). It should also be pointed out here that the reaction did not proceed in the absence of H₂SO₄•SiO₂, which confirmed the effectiveness of the catalyst (entry 1). The proper catalytic dosage of H₂SO₄•SiO₂ might be 20-40% weight ratio to **1a**, and continuously increasing the catalytic dosage significantly elevated the yield of the product **3a** (Table 2, entries 10 and 11). As a result, 40% weight ratio was chosen for further screening of the reaction time (Table 3).

Table 2. The catalytic dosage screening for the model reaction performed at *ca.* 45 °C for 5 min

Entry	Catalyst dosage (% w/w) ^a	Yield 3a (%) ^b
1	0	0
2	8	31
3	10	46
4	15	67
5	20	69
6	25	78
7	30	79
8	35	80
9	40	83
10	45	87
11	50	95

^a Catalyst dosage referred to the weight ratio of the catalyst to the compound **1a**. ^b The yield of the product **3a** was monitored by ¹H NMR (400 MHz, CDCl₃, 298 K) after beginning the model reaction for 5 min at 45 °C.

After confirming a suitable catalytic dosage of $\text{H}_2\text{SO}_4\cdot\text{SiO}_2$ for the model reaction, the reaction temperature and time were then investigated (Table 3). Increasing the reaction temperature led to a shortening of the reaction time (entries 1-7), and the yields of the product **3a** approached 99% as the temperature elevated to 90 °C for two minutes (entry 10).

Table 3. The temperature and time screening for the model reaction with a $\text{H}_2\text{SO}_4\cdot\text{SiO}_2$ catalyst loading of 40% w/w

Entry	Temp. (°C)	Time (min)	Yield 3a (%) ^a
1	30	5	78
2	40	5	87
3	50	5	87
4	60	5	88
5	70	5	88
6	80	5	95
7	90	5	99
8	90	4	99
9	90	3	99
10	90	2	99
11	90	1	95
12	90	0.5	94

^aReaction conditions: 3-Methyl-6,7-dihydrobenzofuran-4(5*H*)-one (**1a**, 1.0 mmol), 4-chlorobenzaldehyde (**2a**, 0.5 mmol) and $\text{H}_2\text{SO}_4\cdot\text{SiO}_2$ (40% weight ratio to **1a**) were mixed and stirred for 5 min at different temperatures. The yield of the product **3a** was monitored by ¹H NMR (400 MHz, CDCl_3 , 298 K) after beginning the model reaction for a certain time.

To further optimize the conditions, a group of orthogonal experiments L_9 (3^4) was designed and carried out (Table 4). The results indicated the main factor influencing the condensation yields was the reaction time. Both conditions (3.0 min at 100 °C with 20% w/w catalyst dosage or 3.0 min at 90 °C with 40% w/w catalyst dosage) gave satisfactory yields (99%, entry 3 and 9 in Table 4). Finally, the optimal conditions were 3.0 min at 90 °C with 30% w/w catalyst dosage from the three factor-three level orthogonal experiment.

Furthermore, we investigated the influence of the recovered catalyst on the model reaction. After completing the reaction, the product **3a** was extracted with ethanol. Then $\text{H}_2\text{SO}_4\cdot\text{SiO}_2$ was recycled by filtration and dried under vacuum at *ca.* 110 °C for 30 min. The recovered catalyst was then reused for the model reaction of **1a** and **2a**. These steps were repeated for three cycles to give the product **3a** in high yields > 95% (Table 5, entries 1-4). The catalyst showed good catalytic activity with only ~ 20% loss in the product yield after nine successive cycles (entry 7).

Table 4. Orthogonal experiments design and results for the model reaction

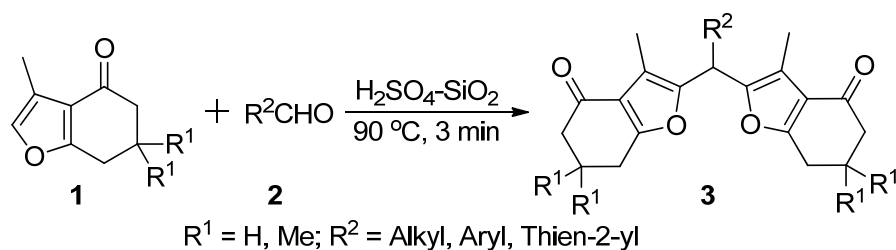
Factor (Level) Entry	Catalyst dosage (% w/w)	Time (min)	Temp. (°C)	Yield (%)
1	1 (20)	1 (1.0)	1 (80)	76
2	1 (20)	2 (2.0)	2 (90)	91
3	1 (20)	3 (3.0)	3 (100)	99
4	2 (30)	1 (1.0)	2 (90)	93
5	2 (30)	2 (2.0)	3 (100)	95
6	2 (30)	3 (3.0)	1 (80)	96
7	3(40)	1 (1.0)	3 (100)	87
8	3(40)	2 (2.0)	1 (80)	93
9	3(40)	3 (3.0)	2 (90)	99
k ₁ ^a	88.7%	85.3%	88.3%	
k ₂ ^a	94.7%	93.0%	94.3%	
k ₃ ^a	93.0%	98.0%	93.7%	
R	6.0%	12.7%	6.0%	

^a k_i was the average scores of each factor at its different level (i equaled 1, 2, and 3, respectively).

Table 5. Reusability of H₂SO₄•SiO₂ for the model reaction

Entry	Catalyst use	Yield 3a (%) ^a
1	Fresh	99
2	1 st recycle	99
3	2 nd recycle	99
4	3 rd recycle	95
5	4 th recycle	89
6	8 th recycle	87
7	9 th recycle	80

^a Reaction conditions: 3-Methyl-6,7-dihydrobenzofuran-4(5*H*)-one (**1a**, 1.0 mmol), 4-chloro-benzaldehyde (**2a**, 0.5 mmol) and H₂SO₄•SiO₂ (30% weight ratio to **1a**) were mixed and stirred for 3 min at 90 °C, and the yield of **3a** was monitored by ¹H NMR (400 MHz, CDCl₃, 298 K) after beginning the model reaction for three minutes.



Scheme 2. The synthetic route for the $\text{H}_2\text{SO}_4\cdot\text{SiO}_2$ -catalyzed condensation reaction.

With the optimized conditions in hand, the scope of $\text{H}_2\text{SO}_4\cdot\text{SiO}_2$ -promoted solvent-free condensation reaction was extended to the 3-methyl-6,7-dihydrobenzofuran-4(5*H*)-ones **1a** and **1b**³⁰ with other aromatic, aliphatic and heterocyclic aldehydes **2b-2r**. In this manner the bis(2-tetrahydrobenzofuran-4(5*H*)-yl)alkanes **3a-r** were efficiently prepared in the yields of 69-98% (See Scheme 2 and Table 6). It is noteworthy that this reaction proceeded smoothly when paraformaldehyde or paraldehyde was used (**3n**, **3o**).

Table 6. $\text{H}_2\text{SO}_4\cdot\text{SiO}_2$ -catalyzed solvent-free condensation reaction

Compd.	R ¹	R ²	Yield (%) ^a
3a	H	4-ClC ₆ H ₄	98
3b	H	Ph	94
3c	H	9-anthryl	85
3d	H	Thien-2-yl	83
3e	H	2-MeOC ₆ H ₄	86
3f	H	3-HOC ₆ H ₄	82
3g	H	Et	79
3h	H	<i>n</i> -Pr	78
3i	H	<i>n</i> -Hex	69
3j	Me	2-FC ₆ H ₄	87
3k	Me	2-MeOC ₆ H ₄	83
3l	Me	3,5-(<i>t</i> -Bu) ₂ -4-HOC ₆ H ₂	89
3m	Me	Thien-2-yl	81
3n	Me	H	84
3o	Me	Me	79
3p	Me	Et	75
3q	Me	<i>n</i> -Pr	74
3r	Me	<i>n</i> -Hex	70

^a Isolated yields.

In most cases, the (het)aromatic aldehydes gave higher yields than the aliphatic aldehydes (Table 6), which might be attributed to the aromatic stabilizing effects of the carbocation intermediate. On the basis of the experimental results and acid-catalysis related literature,^{18,31} a plausible mechanistic pathway for H₂SO₄•SiO₂-promoted solvent-free condensation reaction can involve protonation of the aldehydes **2** by H₂SO₄•SiO₂ and then electrophilic addition at the C-2 position of the tetrahydrobenzofurans **1** to furnish the products **3**.

Conclusions

H₂SO₄•SiO₂ was successfully employed as a reusable, eco-friendly and efficient catalyst under solvent-free conditions to convert aldehydes and tetrahydrobenzofurans into bis(2-tetrahydrobenzofuranyl)alkanes in high yields. The versatile approach has the advantages of broad functional group compatibility, short reaction times, simple operation and environmentally benign nature. The application of this method to other substrates and exploring the medical usage of the products is now underway.

Experimental Section

Unless otherwise noted, all chemical reagents and materials were purchased from commercial suppliers and used without further purification. The solvents of ethyl acetate and petroleum ether (boiling range, 60-90 °C) were dried by CaCl₂ and distilled immediately before use. Flash column chromatography for purification was performed in a glass column by using 200-300 mesh silica gel. The 3-methyl-6,7-dihydrobenzofuran-4(5*H*)-one derivatives³⁰ (**1a** and **1b**) were prepared as described in the literature.

Melting points were determined with an uncorrected X-4 Digital melting point apparatus. IR spectra were recorded on a PE-983 infrared spectrometer as KBr pellets with absorption in cm⁻¹. NMR spectra were recorded in deuterated chloroform (CDCl₃) as solvent employing tetramethylsilane (TMS) as internal standard on Bruker AVANCE III 400 MHz Plus NMR spectrometer. MS data were measured on API 4000 LC-MS/MS system or Finnigan Trace MS instrument. Elemental analyses were carried out with a Vario EL III elementary analysis instrument.

Preparation of catalyst: to a mixture of silica gel (10 g, 200-300 mesh) in dry Et₂O (50 mL) was added commercial concentrated H₂SO₄ (3 mL) and stirred for 5 min. The solvent was evaporated under reduced pressure, then dried at *ca.* 110 °C for 3 h to obtain the H₂SO₄•SiO₂ as a colorless free flowing powder.

General procedure for the synthesis of bis(2-tetrahydrobenzofuranyl)alkanes (**3a-3r**)

An intimate mixture of the 3-methyl-6,7-dihydrobenzofuran-4(5*H*)-one derivative (**1**, 1.0 mmol), aldehyde (**2**, 0.5 mmol) and H₂SO₄•SiO₂ (30% weight ratio to **1**) was vigorously stirred for 2 min at *ca.* 90 °C. After completion of the reaction, the mixture was diluted with EtOH (2 × 5 mL).

After filtrating off the solid catalyst, the filtrate was concentrated to afford crude product, which was further purified by flash column chromatography to yield **3a-3r** (eluent: EtOAc/petroleum ether 1:4 v/v).

2,2'-[(4-Chlorophenyl)methylene]bis[3-methyl-6,7-dihydrobenzofuran-4(5H)-one] (3a).

Yellow blocks, yield 98%, mp 157-158 °C (from CHCl₃); *R_f* 0.22 (EtOAc/petroleum ether 1:4 v/v); ¹H NMR (CDCl₃, 400 MHz) δ: 7.29-7.27 (d, *J* 8.8 Hz, 2H), 7.10 (d, *J* 8.4 Hz, 2H), 5.44 (s, 1H), 2.81 (t, *J* 6.2 Hz, 4H), 2.46 (d, *J* 5.6 Hz, 4H), 2.14 (t, *J* 6.4 Hz, 4H), 2.13 (s, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ: 195.4, 166.1, 147.5, 136.7, 132.8, 129.2, 128.5, 120.8, 115.0, 38.9, 38.1, 23.4, 22.4, 8.7; IR (KBr) *v*: 2948 (m), 2923 (w), 2875 (w), 2864 (w), 1672 (s), 1577 (m), 1490 (m), 1454 (m), 1440 (m), 1412 (m), 1358 (w), 1246 (w), 1089 (w), 1061 (m), 1008 (s), 907 (w), 798 (s); MS (ESI) *m/z*: 867.29 [2M + Na]; Anal. Calcd. For C₂₅H₂₃ClO₄: C, 71.00; H, 5.48; Found: C, 70.88; H, 5.43.

2,2'-(Phenylmethylene)bis[3-methyl-6,7-dihydrobenzofuran-4(5H)-one] (3b).

Yellow blocks, yield 94%, mp 155-156 °C (from CHCl₃); *R_f* 0.26 (EtOAc/petroleum ether 1:4 v/v); ¹H NMR (CDCl₃, 400 MHz) δ: 7.34-7.26 (m, 3H), 7.15 (d, *J* 7.2 Hz, 2H), 5.48 (s, 1H), 2.81 (t, *J* 6.2 Hz, 4H), 2.46 (t, *J* 6.6 Hz, 4H), 2.15 (t, *J* 6.4 Hz, 4H), 2.13 (s, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ: 195.7, 166.2, 148.2, 138.3, 128.6, 127.9, 127.1, 120.9, 115.0, 39.5, 38.2, 23.6, 22.5, 8.9; IR (KBr) *v*: 3029 (w), 2951 (w), 2926 (w), 2886 (w), 1678 (s), 1571 (m), 1493 (w), 1451 (m), 1431 (w), 1356 (m), 1294 (m), 1252 (w), 1061 (w), 1008 (w), 899 (w), 733 (s), 700 (s); MS (ESI) *m/z*: 799.35 [2M + Na]; Anal. Calcd. For C₂₅H₂₄O₄: C, 77.30; H, 6.23; Found: C, 77.19; H, 6.18.

2,2'-(Anthracen-9-ylmethylene)bis[3-methyl-6,7-dihydrobenzofuran-4(5H)-one] (3c).

Yellow plates, yield 85%, mp 128-130 °C (from CHCl₃); *R_f* 0.24 (EtOAc/petroleum ether 1:4 v/v); ¹H NMR (CDCl₃, 400 MHz) δ: 7.75 (d, *J* 7.6 Hz, 1H), 7.61 (dd, *J* 8.8, 1.6 Hz, 1H), 7.34 (t, *J* 7.2 Hz, 1H), 7.28-7.17 (m, 6H), 6.79 (s, 1H), 5.30 (s, 1H), 2.79 (t, *J* 6.0 Hz, 2H), 2.67-2.62 (m, 2H), 2.48 (t, *J* 6.0 Hz, 2H), 2.41 (t, *J* 6.0 Hz, 2H), 2.18 (s, 3H), 2.15 (t, *J* 6.6 Hz, 2H), 2.10 (s, 3H), 2.05 (t, *J* 6.4 Hz, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ: 195.7, 195.4, 166.3, 166.2, 150.1, 147.7, 138.8, 136.9, 135.6, 134.9, 134.7, 128.1, 127.6, 127.4, 127.3, 127.2, 127.1, 125.9, 123.5, 121.5, 120.8, 118.4, 114.6, 112.2, 41.1, 38.3, 38.2, 23.5, 23.4, 22.4, 22.4, 9.7, 9.0; IR (KBr) *v*: 3060 (w), 3018 (w), 2948 (w), 1672 (s), 1574 (m), 1454 (m), 1431 (m), 1412 (w), 1381 (w), 1353 (w), 1064 (s), 1005 (s), 781 (s), 758 (s); MS (ESI) *m/z*: 999.20 [2M + Na]. Anal. Calcd. For C₃₃H₂₈O₄: C, 81.12; H, 5.78; Found: C, 81.01; H, 5.72.

2,2'-(Thiophen-2-ylmethylene)bis[3-methyl-6,7-dihydrobenzofuran-4(5H)-one] (3d).

Yellow blocks, yield 83%, mp 129-131 °C (from CHCl₃); *R_f* 0.25 (EtOAc/petroleum ether 1:4 v/v); ¹H NMR (CDCl₃, 400 MHz) δ: 7.22 (dd, *J* 5.2, 1.2 Hz, 1H), 6.94 (dd, *J* 5.2, 3.6 Hz, 1H), 6.80 (dt, *J* 3.6, 1.2 Hz, 1H), 5.66 (s, 1H), 2.83 (t, *J* 6.0 Hz, 4H), 2.48-2.44 (m, 4H), 2.18 (s, 6H), 2.14 (t, *J* 6.4 Hz, 4H); ¹³C NMR (CDCl₃, 100 MHz) δ: 195.6, 166.2, 147.7, 141.5, 126.7, 125.7, 125.0, 120.9, 114.9, 38.2, 38.2, 23.5, 22.5, 8.9; IR (KBr) *v*: 3094 (w), 2945 (w), 2923 (w), 1675 (s), 1577 (m), 1457 (m), 1434 (m), 1409 (w), 1381 (w), 1356 (w), 1246 (w), 1064 (s), 1005 (s), 901 (m), 722 (w); MS (ESI) *m/z*: 811.19 [2M + Na]. Anal. Calcd. For C₂₃H₂₂O₄S: C, 70.03; H, 5.62; Found: C, 69.91; H, 5.58.

2,2'-[(2-Methoxyphenyl)methylene]bis[3-methyl-6,7-dihydrobenzofuran-4(5H)-one] (3e).

Yellow blocks, yield 86%, mp 164-166 °C (from CHCl₃); *R_f* 0.27 (EtOAc/petroleum ether 1:4 v/v); ¹H NMR (CDCl₃, 400 MHz) δ: 7.33 (dd, *J* 7.6, 1.6 Hz, 1H), 7.24 (dd, *J* 7.6, 1.2 Hz, 1H), 6.93 (td, *J* 7.6, 1.2 Hz, 1H), 6.87 (t, *J* 8.0 Hz, 1H), 5.91 (s, 1H), 3.81 (s, 3H), 2.81 (t, *J* 6.4 Hz, 4H), 2.43 (t, *J* 6.4 Hz, 4H), 2.11 (t, *J* 6.6 Hz, 4H), 2.09 (s, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ: 195.8, 165.8, 156.2, 148.4, 129.5, 128.3, 126.9, 120.9, 120.4, 114.2, 110.4, 55.6, 38.2, 32.8, 23.6, 22.5, 8.7; IR (KBr) ν: 2945 (m), 2836 (w), 1672 (s), 1583 (m), 1493 (m), 1457 (m), 1434 (w), 1283 (s), 1243 (w), 1103 (m), 1064 (m), 1011 (s), 901 (m), 761 (m), 697 (w); MS (ESI) *m/z*: 859.41 [2M + Na]; Anal. Calcd. For C₂₆H₂₆O₅: C, 74.62; H, 6.26; Found: C, 74.49; H, 6.20.

2,2'-[(3-Hydroxyphenyl)methylene]bis[3-methyl-6,7-dihydrobenzofuran-4(5H)-one] (3f).

Yellow oil, yield 82%; *R_f* 0.20 (EtOAc/petroleum ether 1:4 v/v); ¹H NMR (CDCl₃, 400 MHz) δ: 7.17 (t, *J* 7.6 Hz, 1H), 6.75 (dd, *J* 8.0, 2.0 Hz, 1H), 6.68 (d, *J* 8.0 Hz, 1H), 6.64 (s, 1H), 6.17 (brs, 1H), 5.42 (s, 1H), 2.81 (t, *J* 6.0, 4H), 2.45 (t, *J* 6.4 Hz, 4H), 2.13 (s, 6H), 2.12 (t, *J* 6.4 Hz, 4H); ¹³C NMR (CDCl₃, 100 MHz) δ: 196.0, 166.4, 156.2, 148.1, 139.9, 129.7, 120.9, 119.9, 115.1, 115.0, 114.2, 39.3, 38.1, 23.5, 22.5, 8.9; IR (KBr) ν: 3385 (w), 3018 (w), 2945 (w), 2867 (w), 1672 (s), 1602 (m), 1580 (m), 1485 (m), 1454 (s), 1358 (w), 1274 (w), 1246 (w), 1190 (w), 1067 (s), 1008 (s), 904 (m), 758 (m); MS (ESI) *m/z*: 831.21 [2M + Na]. Anal. Calcd. For C₂₅H₂₄O₅: C, 74.24; H, 5.98; Found: C, 74.18; H, 5.92.

2,2'-(Propane-1,1-diyl)bis[3-methyl-6,7-dihydrobenzofuran-4(5H)-one] (3g).

Yellow needles, yield 79%, mp 100-102 °C (from CHCl₃); *R_f* 0.27 (EtOAc/petroleum ether 1:4 v/v); ¹H NMR (CDCl₃, 400 MHz) δ: 3.91 (t, *J* 8.0 Hz, 1H), 2.82 (t, *J* 6.0 Hz, 4H), 2.46-2.42 (m, 4H), 2.15 (s, 6H), 2.14-2.02 (m, 6H), 0.87 (t, *J* 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ: 195.7, 165.6, 149.6, 120.84, 113.4, 38.2, 35.7, 24.8, 23.5, 22.5, 12.1, 8.7; IR (KBr) ν: 2973 (w), 2954 (m), 2917 (w), 2867 (w), 2856 (w), 1692 (s), 1574 (s), 1457 (m), 1428 (m), 1403 (m), 1384 (w), 1358 (w), 1277 (s), 1249 (s), 1064 (m), 1005 (w), 899 (w), 876 (w), 828 (m); MS (ESI) *m/z*: 703.23 [2M + Na]; Anal. Calcd. For C₂₁H₂₄O₄: C, 74.09; H, 7.11; Found: C, 73.99; H, 7.03.

2,2'-(Butane-1,1-diyl)bis[3-methyl-6,7-dihydrobenzofuran-4(5H)-one] (3h).

Yellow needles, yield 78%, mp 103-105 °C (from CHCl₃); *R_f* 0.30 (EtOAc/petroleum ether 1:4 v/v); ¹H NMR (CDCl₃, 400 MHz) δ: 4.03 (t, *J* 8.0 Hz, 1H), 2.84-2.80 (m, 4H), 2.46-2.41 (m, 4H), 2.15 (s, 6H), 2.14-2.09 (m, 4H), 2.03-1.96 (m, 2H), 1.27-1.19 (m, 2H), 0.91 (t, *J* 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ: 195.7, 165.1, 149.8, 120.8, 113.2, 38.2, 33.6, 33.5, 23.5, 22.6, 20.6, 13.6, 8.8; IR (KBr) ν: 2951 (m), 2923 (w), 2867 (w), 1670 (s), 1583 (m), 1457 (w), 1431 (w), 1378 (w), 1274 (w), 1241 (w), 1058 (s), 1008 (s); MS (ESI) *m/z*: 731.29 [2M + Na]; Anal. Calcd. For C₂₂H₂₆O₄: C, 74.55; H, 7.39; Found: C, 74.42; H, 7.33.

2,2'-(Heptane-1,1-diyl)bis[3-methyl-6,7-dihydrobenzofuran-4(5H)-one] (3i).

Yellow oil, yield 69%; *R_f* 0.29 (EtOAc/petroleum ether 1:4 v/v); ¹H NMR (CDCl₃, 400 MHz) δ: 3.99 (t, *J* 8.0 Hz, 1H), 2.84-2.80 (m, 4H), 2.46-2.42 (m, 4H), 2.35 (t, *J* 7.6 Hz, 2H), 2.15 (s, 6H), 2.14-2.09 (m, 4H), 2.00 (q, *J* 7.7 Hz, 2H), 1.68-1.59 (m, 2H), 1.34-1.24 (m, 4H), 0.86 (t, *J* 7.8 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ: 195.9, 165.6, 149.9, 120.9, 113.2, 38.2, 33.9, 33.8, 31.6, 31.4, 31.4, 28.8, 28.7, 27.3, 24.6, 23.6, 22.6, 22.5, 22.4, 14.1, 14.0, 8.8; IR (KBr) ν: 2954 (w), 2926 (m),

2856 (w), 1675 (s), 1580 (m), 1454 (m), 1431 (m), 1412 (w), 1384 (w), 1361 (w), 1061 (s), 1011 (s); MS (ESI) m/z : 815.3 [2M + Na]; Anal. Calcd. For $C_{25}H_{32}O_4$: C, 75.73; H, 8.13; Found: C, 75.64; H, 8.08.

2,2'-[(2-Fluorophenyl)methylene]bis[3,6,6-trimethyl-6,7-dihydrobenzofuran-4(5H)-one]

(3j). Yellow needles, yield 87%, mp 175-177 °C (from $CHCl_3$); R_f 0.34 (EtOAc/petroleum ether 1:4 v/v); 1H NMR ($CDCl_3$, 400 MHz) δ : 7.32-7.23 (m, 2H), 7.10 (t, J 7.2 Hz, 1H), 7.04 (t, J 9.2 Hz, 1H), 5.76 (s, 1H), 2.67 (s, 4H), 2.32 (s, 4H), 2.07 (s, 6H), 1.12 (s, 6H), 1.11 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 195.0, 165.1, 161.3, 158.8, 147.4, 130.1, 130.1, 128.9, 128.8, 125.7, 125.5, 124.1, 124.1, 119.8, 115.5, 115.3, 114.8, 52.6, 37.5, 35.0, 33.2, 33.2, 28.6, 28.5, 8.5; IR (KBr) ν : 2959 (m), 2931 (w), 2889 (w), 2870 (w), 1678 (s), 1583 (m), 1487 (m), 1448 (m), 1386 (w), 1227 (m), 1095 (w), 1056 (m), 750 (m); MS (ESI) m/z : 947.29 [2M + Na]; Anal. Calcd. For $C_{29}H_{31}FO_4$: C, 75.30; H, 6.76; Found: C, 75.14; H, 6.71.

2,2'-[(2-Methoxyphenyl)methylene]bis[3,6,6-trimethyl-6,7-dihydrobenzofuran-4(5H)-one]

(3k). Yellow needles, yield 83%, mp 178-180 °C (from $CHCl_3$); R_f 0.36 (EtOAc/petroleum ether 1:4 v/v); 1H NMR ($CDCl_3$, 400 MHz) δ : 7.27-7.22 (m, 2H), 6.92 (td, J 7.6, 0.8 Hz, 1H), 6.87 (d, J 8.8 Hz, 1H), 5.89 (s, 1H), 3.80 (s, 3H), 2.67 (s, 4H), 2.31 (s, 4H), 2.05 (s, 6H), 1.11 (s, 6H), 1.10 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 195.2, 164.9, 156.3, 148.6, 129.5, 128.3, 126.9, 120.5, 119.7, 114.2, 110.5, 55.6, 52.6, 37.5, 35.0, 33.3, 28.6, 28.5, 8.5; IR (KBr) ν : 3001 (m), 2957 (w), 2934 (w), 2870 (w), 1748, 1675 (s), 1557 (m), 1468 (m), 1451 (m), 1437 (m), 1381 (w), 1243 (s), 1103 (w), 1053 (m), 1025 (m), 753 (m), 669 (w); MS (ESI) m/z : 971.28 [2M + Na]; Anal. Calcd. For $C_{30}H_{34}O_5$: C, 75.92; H, 7.22; Found: C, 75.81; H, 7.18.

2,2'-[(3,5-Di-*tert*-butyl-4-hydroxyphenyl)methylene]bis[3,6,6-trimethyl-6,7-

dihydrobenzofuran-4(5H)-one] (3l). Yellow blocks, yield 89%, mp 76-78 °C (from $CHCl_3$); R_f 0.38 (EtOAc/petroleum ether 1:4 v/v); 1H NMR ($CDCl_3$, 400 MHz) δ : 6.89 (s, 2H), 5.39 (s, 1H), 5.16 (s, 1H), 2.69 (s, 2H), 2.68 (s, 2H), 2.34 (s, 2H), 2.33 (s, 2H), 2.10 (s, 6H), 1.37 (s, 18H), 1.13 (s, 6H), 1.12 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 195.2, 165.2, 152.8, 149.0, 135.9, 128.4, 124.5, 119.7, 114.7, 52.6, 39.4, 37.6, 35.1, 34.2, 30.1, 28.8, 28.2, 8.7; IR (KBr) ν : 3548 (w), 3464 (w), 3315 (w), 3021 (m), 3004 (w), 2965 (w), 2864 (w), 1771 (w), 1670 (s), 1577 (m), 1434 (m), 1389 (w), 1358 (w), 1305 (w), 1235 (m), 1199 (w), 1126 (w), 1061 (m), 758 (s), 742 (s), 669 (w); MS (ESI) m/z : 1167.57 [2M + Na]; Anal. Calcd. For $C_{37}H_{48}O_5$: C, 77.59; H, 8.45; Found: C, 77.43; H, 8.40.

2,2'-(Thiophen-2-ylmethylene)bis[3,6,6-trimethyl-6,7-dihydrobenzofuran-4(5H)-one] (3m).

Yellow blocks, yield 81%, mp 151-153 °C (from $CHCl_3$); R_f 0.35 (EtOAc/petroleum ether 1:4 v/v); 1H NMR ($CDCl_3$, 400 MHz) δ : 7.22 (dd, J 5.2, 1.2 Hz, 1H), 6.94 (dd, J 4.8, 3.6 Hz, 1H), 6.77 (dd, J 3.6, 1.2 Hz, 1H), 5.66 (s, 1H), 2.69 (s, 4H), 2.34 (s, 4H), 2.15 (s, 6H), 1.12 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 195.4, 165.3, 148.0, 141.7, 126.7, 125.6, 124.9, 119.8, 114.9, 52.6, 52.6, 37.5, 35.5, 35.0, 28.6, 28.5, 8.8; IR (KBr) ν : 3321 (w), 3097 (m), 3066 (w), 2954 (w), 2926 (w), 2867 (w), 1672 (s), 1580 (m), 1440 (m), 1386 (w), 1344 (w), 1297 (w), 1266 (w), 1227 (m), 1142 (w), 1056 (m), 969 (w), 862 (w), 828 (w), 764 (m), 750 (w), 728 (w); MS (ESI)

m/z: 923.20 [2M + Na]; Anal. Calcd. For C₂₇H₃₀O₄S: C, 71.97; H, 6.71; Found: C, 71.79; H, 6.67.

2,2'-Methylenebis[3,6,6-trimethyl-6,7-dihydrobenzofuran-4(5H)-one] (3n). Colorless needles, yield 84%, mp 174-176 °C (from CHCl₃); *R_f* 0.38 (EtOAc/petroleum ether 1:4 v/v); ¹H NMR (CDCl₃, 400 MHz) δ: 3.82 (s, 2H), 2.66 (s, 4H), 2.32 (s, 4H), 2.16 (s, 6H), 1.11 (s, 12H); ¹³C NMR (CDCl₃, 100 MHz) δ: 195.0, 164.9, 146.7, 119.8, 114.0, 52.0, 37.4, 35.0, 28.6, 22.6, 8.7; IR (KBr) *v*: 2957 (m), 2937 (w), 2870 (w), 1670 (s), 1583 (m), 1442 (m), 1403 (m), 1384 (w), 1347 (w), 1266 (w), 1238 (m), 1140 (w), 1056 (m), 1036 (m), 963 (w); MS (ESI) *m/z*: 759.29 [2M + Na]; Anal. Calcd. For C₂₃H₂₈O₄: C, 74.97; H, 7.66; Found: C, 74.81; H, 7.60.

2,2'-(Ethane-1,1-diyl)bis[3,6,6-trimethyl-6,7-dihydrobenzofuran-4(5H)-one] (3o). Colorless blocks, yield 79%, mp 195-197 °C (from CHCl₃); *R_f* 0.39 (EtOAc/petroleum ether 1:4 v/v); ¹H NMR (CDCl₃, 400 MHz) δ: 4.20 (q, *J* 7.2 Hz, 1H), 2.68 (s, 4H), 2.31 (s, 4H), 2.09 (s, 6H), 1.59 (d, *J* 7.2 Hz, 3H), 1.12 (s, 12H); ¹³C NMR (CDCl₃, 100 MHz) δ: 195.1, 164.6, 150.8, 119.7, 112.5, 52.6, 37.5, 35.0, 28.0, 28.7, 28.5, 17.4, 8.5; IR (KBr) *v*: 2957 (m), 2928 (w), 2875 (w), 1670 (s), 1580 (m), 1448 (m), 1406 (m), 1384 (w), 1367 (m), 1350 (m), 1302 (w), 1271 (w), 1232 (w), 1056 (m), 1028 (m), 963 (w); MS (ESI) *m/z*: 787.31 [2M + Na]; Anal. Calcd. For C₂₄H₃₀O₄: C, 75.36; H, 7.91; Found: C, 75.22; H, 7.87.

2,2'-(Propane-1,1-diyl)bis[3,6,6-trimethyl-6,7-dihydrobenzofuran-4(5H)-one] (3p). Colorless needles, yield 75%, mp 155-157 °C (from CHCl₃); *R_f* 0.37 (EtOAc/petroleum ether 1:4 v/v); ¹H NMR (CDCl₃, 400 MHz) δ: 3.90 (t, *J* 8.0 Hz, 1H), 2.69 (s, 4H), 2.32 (s, 4H), 2.13 (s, 6H), 2.04 (t, *J* 7.6 Hz, 2H), 1.21 (s, 12H), 0.85 (t, *J* 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ: 195.1, 164.7, 149.9, 119.6, 113.3, 52.6, 37.5, 36.0, 35.0, 28.7, 28.5, 24.9, 12.0, 8.6; IR (KBr) *v*: 2965 (m), 2923 (w), 2872 (w), 1667 (s), 1583 (m), 1442 (m), 1381 (m), 1274 (m), 1232 (m), 1061 (w); MS (ESI) *m/z*: 815.31 [2M + Na]; Anal. Calcd. For C₂₅H₃₂O₄: C, 75.73; H, 8.13; Found: C, 75.59; H, 8.08.

2,2'-(Butane-1,1-diyl)bis[3,6,6-trimethyl-6,7-dihydrobenzofuran-4(5H)-one] (3q). Yellow plates, yield 74%, mp 142-143 °C (from CHCl₃); *R_f* 0.37 (EtOAc/petroleum ether 1:4 v/v); ¹H NMR (CDCl₃, 400 MHz) δ: 4.02 (t, *J* 8.0 Hz, 1H), 2.68 (s, 4H), 2.31 (s, 4H), 2.13 (s, 6H), 2.13-1.96 (m, 2H), 1.27-1.18 (m, 2H), 1.12 (s, 12H), 0.91 (s, *J* 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ: 195.1, 164.7, 150.1, 119.6, 113.1, 52.6, 37.5, 35.0, 33.9, 33.6, 28.7, 28.5, 20.6, 13.6, 8.7; IR (KBr) *v*: 2959 (m), 2931 (w), 2872 (w), 1664 (s), 1583 (m), 1440 (m), 1381 (m), 1274 (m), 1050 (w); MS (ESI) *m/z*: 843.36 [2M + Na]; Anal. Calcd. For C₂₆H₃₄O₄: C, 76.06; H, 8.35; Found: C, 75.88; H, 8.29.

2,2'-(Heptane-1,1-diyl)bis[3,6,6-trimethyl-6,7-dihydrobenzofuran-4(5H)-one] (3r). Yellow plates, yield 70%, mp 116-117 °C (from CHCl₃); *R_f* 0.36 (EtOAc/petroleum ether 1:4 v/v); ¹H NMR (CDCl₃, 400 MHz) δ: 3.99 (t, *J* 8.0 Hz, 1H), 2.68 (s, 4H), 2.31 (s, 4H), 2.13 (s, 6H), 2.03-1.97 (m, 2H), 1.31-1.16 (m, 8H), 1.12 (s, 12H), 0.86 (t, *J* 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ: 195.1, 164.7, 150.2, 119.6, 113.1, 52.6, 37.5, 35.0, 34.2, 31.5, 31.5, 28.7, 28.7, 27.3, 22.5, 14.0, 8.7; IR (KBr) *v*: 2959 (m), 2926 (w), 2870 (w), 1667 (s), 1577 (m), 1437 (m), 1271

(m), 1233 (m), 1058 (m), 1015 (w), 962 (w); MS (ESI) m/z : 927.44 [2M + Na]; Anal. Calcd. For C₂₉H₄₀O₄: C, 76.95; H, 8.91; Found: C, 76.77; H, 8.86.

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