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Three-Step One-Pot Process of 3-Methyl-5-Benzofuranol from Amine, Aldehydes, and *p*-Benzoquinone

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ABSTRACT: 3-Methyl-5-benzofuranol was prepared by a one-pot process from morpholine, propionaldehyde, and *p*-benzoquinone in 85−87% isolated yields. Avoiding the tedious multistep isolation and purification operations, this practical and efficient process dramatically enhanced the production efficiency as well as reduced the amount of chemical wastes of reaction. The scale-up results showed that the performance was maintained, suggesting potential large-scale applications. Furthermore, the synthesis strategy showed high efficiency for a wide range of aliphatic aldehydes and ketone derivatives.

KEYWORDS: *benzofuran, 3-methyl-5-benzofuranol, process development, one-pot synthesis*

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INTRODUCTION

3-Methyl-5-benzofuranol (**1**, Figure 1) is a useful compound known as a key intermediate for the preparation of numerous bioactive molecules, such as Caspase-3 inhibitor (**2**, Figure 1),[1] NAD(*P*)H: quinone oxidoreductase 1-directed antitumor quinone substrates (**3**, Figure 1),[2−5] tanshinone IIA (**4**, Figure 1) and its analogues,[6] and TGR5 agonists (**5**, Figure 1).[7] Also, 3-methyl-5-benzofuranol can be used as additives in spices to significantly enhance the aroma of perfumes, textiles, skincare products, and so on.[8] Nowadays, because valuable natural fragrance resources are expensive and scarce, there is an urgent need for new fine chemicals with a steady supply in the market.

Until now, in order to synthesize 3-methyl-5-benzofuranol efficiently and rapidly, two main routes have been widely developed (Scheme 1). Route A: using the expensive 2-acetyl-4-methoxyphenol (**6**) and ethyl bromoacetate (**7**) as starting materials, 3-methyl-5-benzofuranol was prepared via subsequent condensation, hydrolysis, cyclization, and demethylation. The intermediates had to be isolated and purified in several steps through column chromatography purifications and crystallizations. The toxic and hazardous ethyl bromoacetate and boron tribromide brought difficulties in waste disposal. Thus, the total yield was only 31%.[7] Route B: the enamine (**12a** or **12b**) was prepared from secondary amine (piperidine and morpholine) and propionaldehyde and reacted with *p*-benzoquinone (PBQ) in slow addition over 12 h to generate intermediate **13**. Finally, 3-methyl-5-benzofuranol was obtained through the deamination of intermediate **13** in HCl. In this long process, the intermediate enamine needed to be purified by distillation. Also, the reported total yields ranged from 25 to 76%, indicating that the reaction process was difficult to control and repeat.[1,3,8] Compared with route A, route B was conducted using a mild reaction with cheaper raw materials. However, both routes suffered from tedious purification operations of several intermediates in the multistep process, suggesting the impracticability of the large-scale production of 3-methyl-5-benzofuranol.

The "one-pot process" refers to conversion of starting materials into the final target by a series of transformations, even the changing reaction conditions, occurring in the same reactor and avoiding the isolation of any intermediates.[9,10] This approach is very stimulating from the sustainable point of view for the synthesis of 3-methyl-5-benzofuranol because it can be processed without the separation of enamine and intermediate **13** and it improves the repeatability. In some instances, the one-pot method may become feasible if the reactants, products, solvents, and reagents do not interfere with each other during the process. Herein, via the investigation of the effects of solvent, the additive et al. of the route B, the synthesis of 3-methyl-5-benzofuranol was carried out using a practical and efficient one-pot process, which showed a potential application in large-scale production.

RESULTS AND DISCUSSION

The Synthesis of Enamine 12a. In the first step reaction, the method of the synthesis of enamine from morpholine and propionaldehyde was investigated. In You's work,[2,4] the mole ratio of morpholine to propionaldehyde was 2.4. However, in our experiment, the excess morpholine in the system was incompletely removed via vacuum distillation, and the poor stability of the resulted enamine led to the low yield. In the subsequent treatment with PBQ, only a small amount of the desired product was generated in the presence of residual

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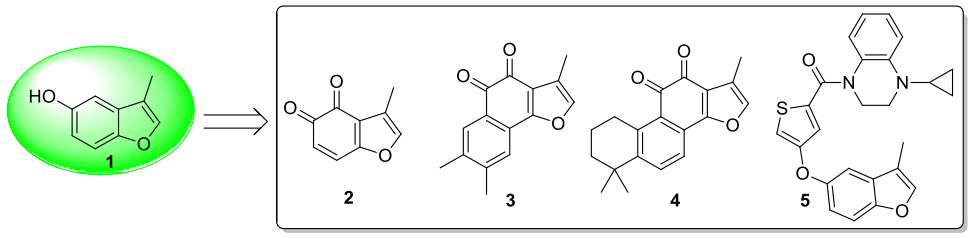
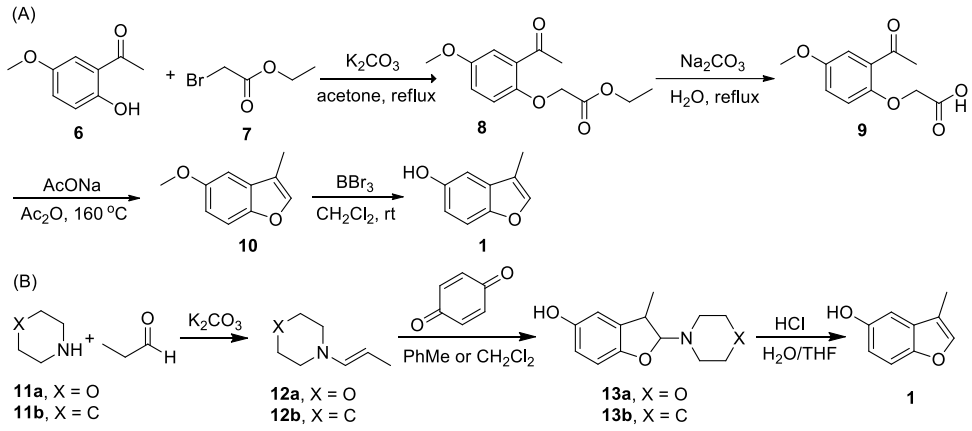


Figure 1. Structure of 3-methyl-5-benzofuranol and bioactive derivatives.

Scheme 1. Process Routes of 3-Methyl-5-Benzofuranol

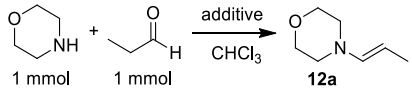


morpholine in enamine. Thus, multiple distillation purifications were required. Even if the pure enamine was used, the reaction was not satisfactory because of the formation of the byproduct (*p*-phenol) in the system, and the yield of **13a** was only 80%.

To avoid the difficult separation, the problem from excess morpholine must be solved. The amount of propionaldehyde was increased to consume the morpholine completely. However, a small amount of morpholine residue was still observed with 1.5 equivalents of aldehyde. While the use of 3.0 equivalents of aldehyde led to no residual morpholine, the product was accompanied by 20% impurities (Table S1). Then, various additives on the synthesis of **12a** were screened under the condition of an equivalent amount of morpholine and propionaldehyde in $CHCl_3$. In Table 1, 4 Å molecular sieves (4 Å MS) and anhydrous $MgSO_4$ were selected as water adsorbents in the reaction. Though the performance of the former was better than that of the latter, the increased amount of 4 Å MS did not improve the yield, which was leveled around 74% (entries 1−4, Table 1). No product was formed in the presence of $TiCl_4$, while the yield was 69% over K_2CO_3 (entries 5, 6, Table 1). $Ti(OPr^i)_4$ was used in the preparation of the imine.[11,12] In our reaction, using $Ti(OPr^i)_4$ as an additive, the yield of enamine was up to 87% without residual morpholine (entry 7, Table 1). To our delight, when 1.0 equiv. of $Ti(OPr^i)_4$ was employed, enamine could be obtained in more than 99% yield (entry 9, Table 1). In addition, the feeding sequence influenced the yield of enamine synthesis, and adding the mixture of propionaldehyde and $Ti(OPr^i)_4$ in a dropwise manner to the solution of morpholine in an ice bath (Table S2) presented the best yield.

Considering the toxic $CHCl_3$ and its limitation in the industry, several solvents including EtOAc, CH_2Cl_2, tetrahydrofuran (THF), 2-Me-THF, dimethylformamide (DMF), CH_3CN, toluene, and *n*-hexane were tested. CH_2Cl_2 and

Table 1. Effect of Different Additives on the Synthesis of Enamine[a]



entry	additive	amount	yield of the product (%)[b]	yield of the byproduct (%)[b]
1	4 Å MS	1.0 g	73	
2	4 Å MS	1.5 g	73	
3	4 Å MS	2.0 g	74	
4	$MgSO_4$	1.0 g	<50	
5	$TiCl_4$	0.5 mmol	0	70
6	K_2CO_3	0.5 mmol	69	1
7	$Ti(OPr^i)_4$	0.5 mmol	87	13
8	$Ti(OPr^i)_4$	0.75 mmol	97	3
9	$Ti(OPr^i)_4$	1.0 mmol	>99	0

[a]Reaction conditions: morpholine (1 mmol) diluted with $CHCl_3$, propionaldehyde (1 mmol), and additives was added in the ice bath, stirred at 0 °C for 30 min, then reacted at room temperature for 2 h. [b]The yield was determined with GC area normalization.

THF were proved to be the appropriate solvents for this conversion (entries 1−8, Table 2). As shown in Tables S3−S4 and Table 2, both CH_2Cl_2 and THF were investigated in subsequent experiments, and the latter was more acceptable in the process. In THF, the yield could reach over 99% in 10 min at 0 °C (entry 10, Table 2). However, elevated temperature or prolonged reaction time decreased the yield because of the formation of side products (entries 11−14, Table 2).

The Synthesis of 13a. With the optimum conditions for the synthesis of enamine **12a** in hand, PBQ (1.0 equiv.) was directly added to the above mentioned enamine solution (entry 1, Table 2). The mixture was stirred for 20 min, and then the black precipitate was filtered and washed with

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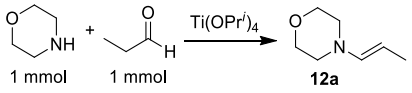
Table 2. Optimization of Reaction Conditions for the Synthesis of Enamine with $Ti(OPr^i)_4$ as the Additive



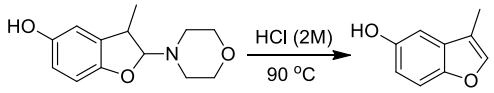
entry	solvent	T (°C)	time (min)	yield of the product (%)[a]	yield of the byproduct (%)[a]
1	EtOAc	0	30	88	8
2	CH_2Cl_2	0	30	93	4
3	THF	0	30	92	3
4	2-Me-THF	0	30	80	8
5	DMF	0	30	58	12
6	CH_3CN	0	30	50	20
7	toluene	0	30	83	6
8	*n*-hexane	0	30	85	5
9	THF	0	5	93	0
10	THF	0	10	99	1
11	THF	0	15	97	3
12	THF	0	20	94	6
13	THF	25	10	97	3
14	THF	40	10	85	15

[a]The yield was determined with GC area normalization.

dichloromethane. The solvent was distilled, and the residue was purified by column chromatography to obtain product **13a** with 88% isolated yields. As seen from Table 3, the amount of PBQ changing in the range of 1.0 to 1.5 equivalents had a little influence on the yield (entries 1−3, Table 3). When the reaction was conducted at −10, 25, and 50 °C, the reaction performance was not as good as at 0 °C. The reaction at room temperature or above led to the formation of *p*-phenol and decrease of yield (entries 1 and 5−6, Table 3). Based on the optimization, the reaction could be completed in 20 min with 1.0 equivalent PBQ in 88% yield (entry 1, Table 3), and the yield remained the same even after further increasing of the reaction time.

Deamination. In Table 4, the effects of solvents, amount of acid, and reflux time on the reaction were investigated. According to Snyder's work,[13] the compound **13a** could smoothly convert to the desired product **1** in an excellent yield in THF with 5.0 equivalents amount of 2 M aqueous HCl

Table 4. Optimization of Reaction Conditions for Deamination



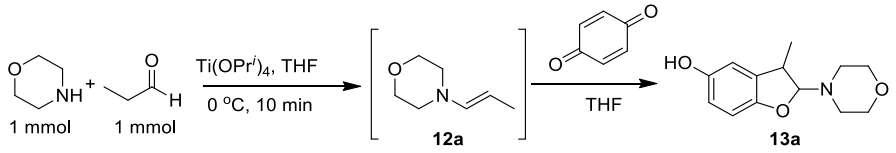
entry	solvent	HCl (eq)	time (h)	yield (%)[a]
1	THF	5.0	2.0	97
2	acetone	5.0	2.0	83
3	EtOAc	5.0	2.0	
4	toluene	5.0	2.0	
5	THF	1.0	2.0	81
6	THF	1.5	2.0	89
7	THF	2.0	2.0	97
8	THF	3.0	2.0	97
9	THF	10	2.0	96
10	THF	2.0	0.5	51
11	THF	2.0	1.0	74
12	THF	2.0	1.5	90

[a]Isolated yields.

(entry 1, Table 4). Compared with the case of THF as the solvent, the yield of **1** decreased slightly in acetone (entry 2, Table 4). Unfortunately, the resulted mixture was a two-phase system when toluene or ethyl acetate was used as the solvent, and only a trace amount of the product was obtained because of the limited mass transfer (entries 3 and 4, Table 4). In THF, using 2.0 equivalents of HCl (2 M) afforded **1** in comparable yield (entry 7, Table 4). Furthermore, a reaction time of 2 h was essential because shortening the reaction time made the conversion of **13a** incomplete, resulting in a decreased yield (entries 10−12, Table 4).

One-Pot Synthesis of 3-Methyl-5-Benzofuranol. Encouraged by these results, three-step one-pot synthesis of 3-methyl-5-benzofuranol was investigated. As a result, in Table 5, the "one-pot method" experiment was carried out on the scale of 10 mmol with the total yield of 89% (entry 1), which was higher than the overall yield of the step-by-step reaction. Moreover, the "one-pot method" dramatically enhanced the production efficiency through avoiding the tedious multistep isolation and purification operations. In order to verify the scale-up effect and industrial value of the one-pot process for

Table 3. Optimization of Reaction Conditions of Enamine with PBQ



entry	PBQ (mmol)	T (°C)	time (min)	yield (%)[a]
1	1.0	0	20	88
2	1.25	0	20	87
3	1.5	0	20	88
4	1.0	−10	20	59
5	1.0	25	20	84
6	1.0	50	20	75
7	1.0	0	10	79
8	1.0	0	30	87
9	1.0	0	60	85

[a]Isolated yields.

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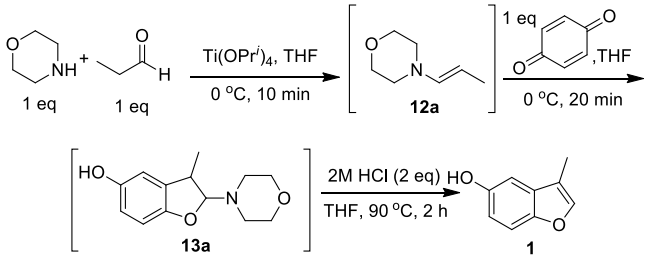
Table 5. One-Pot Process for the Preparation of 3-Methyl-5-Benzofuranol (1)[a]



entry	scale (mol)	yield (%)[b]
1	0.01	89
2	0.1	88
3	1.0	85
4	1.0	87
5	1.0	87

[a]Reaction conditions: a solution of propionaldehyde in THF added dropwise to the solution of morpholine in THF at 0 °C and stirred for 10 min. A solution of PBQ in THF was dropped into the reaction mixture with stirring for 20 min at 0 °C. Then, HCl aqueous was added to the reaction mixture over 15 min, and the reaction mixture was heated to 90 °C and stirred for 2 h. [b]Isolated yields.

the preparation of 3-methyl-5-benzofuranol, the scale of the reaction was enlarged to 1.0 mol, and 85−87% isolated yields for parallel batches were obtained (entries 3−5, Table 5). Almost no obvious scale-up effect occurred in the one-pot process under the current scale, which showed potential in industrial scale-up. Furthermore, the recovery rate of solvent THF was still more than 90%, which greatly reduced the cost of the solvent and the production of chemical wastes. Compared with the previous method, this one-pot process represented a 52% reduction in the Process Mass Intensity (PMI) (Table S5).

Substrates Scope of the One-Pot Process. To test the generality of the established method, the substrate scope was investigated. In Table 6, various aliphatic aldehydes could convert to corresponding 3-substituted-5-benzofuranol with the isolated yields of 79−84% (entries 1−4, Table 6). Interestingly, aliphatic ketones were also acceptable in this protocol. Acetone could be successfully transformed to 2-methyl-5-benzofuranol (**15e**), and cyclic ketones, such as cyclohexanone and cycloheptanone, could also be well converted to the desired products with moderate yields (entries 5−8, Table 6). This one-pot process provided a promising method for the synthesis of the derived compounds.

CONCLUSIONS

We have developed an efficient and scalable one-pot process for the preparation of 3-methyl-5-benzofuranol with 85−87% isolated yields. The complicated workup procedure and reaction time were optimized comprehensively. More importantly, the production of liquid waste was dramatically reduced in the current process. Moreover, various aliphatic aldehydes and aliphatic ketones could convert to the corresponding products smoothly in this protocol. Compared with the previously reported methods, the newly developed process was of low cost and had a simple operation and high efficiency.

EXPERIMENTAL SECTION

General. All reagents were commercially available and used without any further purification unless otherwise noted. ^{1}H NMR spectra were recorded on a Bruker 400 MHz instrument. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane or referenced to residual solvent. Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane or referenced to residual solvent. Data are represented as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constants in Hertz (Hz). High-resolution mass spectrometry (electrospray ionization, ESI) were carried out using a Waters Quatro Macro triple quadrupole mass spectrometer Mass spectra (EI) were measured on a Waters Micromass GCT spectrometer. GC analysis was performed on an Echrom A90 gas chromatograph equipped with a flame ionization detector using a fused silica capillary column. Analytical HPLC (Shimadzu LC20) analysis was carried out on a C18 reversed-phase analytical column (150 mm × 4.6 mm, particle size 5 μm) at 30 °C using mobile phases 68% (pure water) and 32% (acetonitrile) at a flow rate of 1.0 mL min^{-1}. Inductively coupled plasma−optical emission spectrometry (ICP-OES) analysis was carried out on Agilent 725 ICP-OES.

One-Pot Preparation of 3-Methyl-5-benzofuranol (1). A solution of propionaldehyde (58 g, 1.0 mol) and Ti(OPr^i)$_4$ (284 g, 1.0 mol) in THF (500 mL) was added dropwise to the solution of morpholine (86 g, 1.0 mol) in THF (500 mL) at 0 °C and stirred for 10 min. A solution of PBQ (108 g, 1.0 mol) in THF (500 mL) was dropped into the reaction mixture with stirring for 20 min at 0 °C. Then, HCl aqueous (2 M, 1 L) was added to the reaction mixture over 15 min, and the reaction mixture was heated to 90 °C and stirred for 2 h. After the reaction was complete, the white suspension formed (of TiO_2) was filtered through Celite. The residue was concentrated via a rotatory evaporator in vacuo to recover THF. Then, the residue reaction solution was extracted with ethyl acetate (500 mL × 3), The organic layers were combined and concentrated to give a light purple solid, which was further purified by recrystallization from dichloromethane to give the product (**1**) as a white solid (129 g, 87% for three steps). The purity was 99.4%, as determined by HPLC. m.p. 91−93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38 (d, J = 0.6 Hz, 1H), 7.30 (d, J = 8.8 Hz, 1H), 6.93 (d, J = 2.5 Hz, 1H), 6.82 (dd, J = 8.8, 2.5 Hz, 1H), 5.37 (s, 1H), 2.16 (d, J = 1.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 151.1, 150.3, 142.5, 130.0, 115.5, 112.7, 118.8, 104.7, 7.9. HRMS (ESI) m/z calcd for $C_9H_8O_2$ [M + H]$^+$: 148.0524, found: 148.0558.

Procedure for Synthesis of 15a-h. A solution of aldehydes or ketones (2.0 mmol) and Ti(OPr^i)$_4$ (568 mg, 2.0 mol) in THF (1 mL) was added dropwise to the solution of morpholine (172 mg, 2.0 mmol) in THF (1 mL) at 0 °C and stirred for 10 min. A solution of PBQ (216 mg, 2.0 mmol) in THF (1 mL) was dropped into the reaction mixture with stirred for 20 min at 0 °C. Then, HCl aqueous (2 M, 2 mL) was added to the reaction mixture, and the reaction mixture was heated to 90 °C and stirred for 2 h. After the reaction was complete, water (5 mL) and ethyl acetate (10 mL) were added, and the white suspension formed (of TiO_2) was filtered through Celite. The residue was washed with ethyl acetate (2 × 10 mL). The organic layers were combined and

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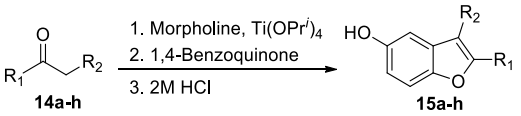
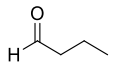
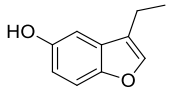
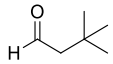
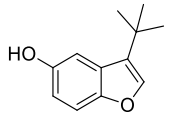
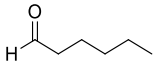
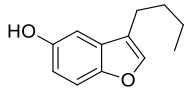
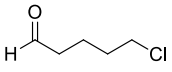
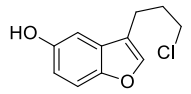
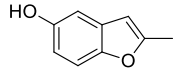
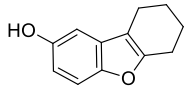
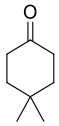
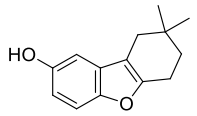
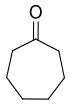
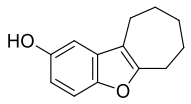
Table 6. Substrates Scope of the One-Pot Process[a]



entry	substrate	product		yield (%)[b]
1			**15a**	84
2			**15b**	79
3			**15c**	82
4			**15d**	80
5			**15e**	65
6			**15f**	76
7			**15g**	75
8			**15h**	78

[a]The reagent dosage and reaction conditions are the same as the one-pot process for the preparation of 3-methyl-5-benzofuranol. [b]Isolated yields.

concentrated to give the crude product, which was further purified by silica column chromatography (petroleum ether/ethyl acetate = 5:1) to afford **15a-h**.

3-Ethyl-5-benzofuranol (15a). White solid. m.p. 102−104 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35 (s, 1H), 7.28 (d, J = 8.8 Hz, 1H), 6.96 (d, J = 2.4 Hz, 1H), 6.81 (dd, J = 8.8, 2.4 Hz, 1H), 6.13 (s, 1H), 2.57−2.63 (m, 2H), 1.28 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 151.4, 150.3, 141.6, 129.1, 122.2, 112.7, 111.7, 104.7, 21.0, 16.9. HRMS (ESI) m/z calcd for $C_{10}H_{10}O_2$ $[M + H]^+$: 162.0681, found: 162.0652.

3-(*tert*-Butyl)-5-benzofuranol (15b). White solid. m.p. 124−126 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31 (s, 1H), 7.30 (d, J = 7.1 Hz, 1H), 7.16 (d, J = 2.4 Hz, 1H), 6.80 (dd, J = 8.7, 2.4 Hz, 1H), 5.53 (s, 1H), 1.38 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 150.0, 149.6, 139.4, 129.0, 126.6, 111.3, 110.9, 105.9, 29.8, 28.7 (3C). HRMS (ESI) m/z calcd for $C_{12}H_{14}O_2$ $[M + H]^+$: 190.0994, found: 190.0962.

3-Butyl-5-benzofuranol (15c). Pale yellow solid. m.p. 121−123 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36 (s, 1H), 7.29 (d, J = 8.7 Hz, 1H), 6.96 (d, J = 2.6 Hz, 1H), 6.79 (dd, J = 8.7, 2.6 Hz, 1H), 5.24 (s, 1H), 2.57−2.61 (m, 2H), 1.62−1.69 (m, 2H), 1.36−1.43 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 151.1, 150.4, 142.1, 129.3, 120.5, 112.6, 111.8, 104.8, 31.1, 23.2, 22.5, 13.9. HRMS (ESI) m/z calcd for $C_{12}H_{14}O_2$ $[M + H]^+$: 190.0994, found: 190.0975.

3-(3-Chloropropyl)-5-benzofuranol (15d). White solid. m.p. 140−142 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 (s, 1H), 7.28 (d, J = 8.7 Hz, 1H), 6.95 (d, J = 2.4 Hz, 1H), 6.82 (dd, J = 8.7, 2.4 Hz, 1H), 3.54 (t, J = 6.3 Hz, 2H), 2.75 (t, J = 7.1 Hz, 2H), 2.05−2.11 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 151.6, 150.3, 142.5, 128.8, 118.6, 113.0, 111.9, 104.6, 44.3, 31.6, 20.5. HRMS (ESI) m/z calcd for $C_{11}H_{11}ClO_2$ $[M + H]^+$: 210.0448, found: 210.0490.

2-Methyl-5-benzofuranol (15e). White solid. m.p. 102−104 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.23 (d, J = 8.7 Hz, 1H), 6.88 (d, J = 2.6 Hz, 1H), 6.70 (dd, J = 8.7, 2.6 Hz, 1H), 6.27 (s, 1H), 5.02 (s, 1H), 2.42 (d, J = 0.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.5, 150.3, 148.7, 129.0, 110.3, 109.9, 104.3, 101.5, 13.1. HRMS (ESI) m/z calcd for $C_9H_8O_2$ $[M + H]^+$: 148.0524, found: 148.0501.

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6,7,8,9-Tetrahydrodibenzo[*b*,*d*]furan-2-ol (15f). Pale yellow solid. m.p. 97−99 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.23 (d, J = 8.6 Hz, 1H), 6.82 (d, J = 2.6 Hz, 1H), 6.69 (dd, J = 8.6, 2.6 Hz, 1H), 4.98 (s, 1H), 2.69−2.72 (m, 2H), 2.54−2.57 (m, 2H), 1.89−1.93 (m, 2H), 1.80−1.86 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 154.2, 150.1, 148.2, 128.7, 111.7, 110.0, 109.9, 102.9, 22.5, 21.9, 21.6, 19.4. HRMS (ESI) m/z calcd for $C_{12}H_{12}O_2$ $[M + H]^+$: 188.0837, found: 188.0881.

8,8-Dimethyl-6,7,8,9-tetrahydrodibenzo[*b*,*d*]furan-2-ol (15 g). Pale yellow solid. m.p. 117−119 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.20 (d, J = 8.6 Hz, 1H), 6.79 (d, J = 2.5 Hz, 1H), 6.68 (dd, J = 8.6, 2.5 Hz, 1H), 5.58 (s, 1H), 2.66−2.69 (m, 2H), 2.29 (s, 2H), 1.64 (t, J = 6.4 Hz, 2H), 1.01 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 154.1, 151.2, 149.7, 130.1, 112.2, 111.1, 111.0, 103.9, 35.9, 34.3, 30.2, 28.0 (2C), 21.0. HRMS (ESI) m/z calcd for $C_{14}H_{16}O_2$ $[M + H]^+$: 216.1150, found: 216.1103.

7,8,9,10-Tetrahydro-6*H*-cyclohepta[*b*]benzofuran-2-ol (15h). Dark gray solid. m.p. 99−101 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.18 (d, J = 8.6 Hz, 1H), 6.81 (d, J = 2.5 Hz, 1H), 6.70 (dd, J = 8.6, 2.5 Hz, 1H), 5.70 (s, 1H), 2.88 (t, J = 5.5 Hz, 2H), 2.59 (t, J = 5.4 Hz, 2H), 1.77−1.85 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.6, 151.2, 148.2, 131.4, 115.8, 111.1, 110.8, 103.7, 30.5, 29.2, 28.2, 26.3, 23.2. HRMS (ESI) m/z calcd for $C_{13}H_{14}O_2$ $[M + H]^+$: 202.0994, found: 202.0958.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.0c00507.

Experiment optimization, one-pot protocol, PMI calculation, HPLC and ICP-OES analysis, and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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