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A Concise Synthesis of Potential COX Inhibitor BRL-37959 and Analogs Involving Bismuth(III) Catalyzed Friedel-Crafts Acylation

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We report the development of a concise method of synthesizing possible cyclooxygenase (COX) inhibitor BRL-37959, which is believed could be a potent nonsteroidal anti-inflammatory drug (NSAID). The four-step synthesis greatly increases the efficiency of compound production from commercially available salicylaldehydes. The synthesis involves an optimized, bismuth(III) tirfluoromethanesulfonate catalyzed, benzoylation of the benzofuran ring.

Keywords: NSAID • Benzofuran • Benzoylation • Bismuth(III) trifluoromethanesulfonate

Introduction

The replacement of opioids in post-operative pain is a considerable goal in medicinal chemistry. In 1986, Boyle et al. synthesized BRL-37959 (**5a**) and found that the compound was active as a non-steroidal anti-inflammatory drug (NSAID), with comparable levels of analgesia to morphine. NSAID's are viewed as a potential replacement to opioids for post-operative pain [1]. Zomax, an NSAID which was administered in the 1970's, was used as an alternative due to its non-addictive properties, but was withdrawn from the market in 1983 due to high rates of anaphylactic shock among patients who were prescribed it [2]. Since 1983, no reasonable non-opiate drug has been made available for chronic and postoperative pain. BRL-37959 may be used as an alternative NSAID, in hopes to reduce the number of opioids which are prescribed daily.

As of today, BRL-37959 has not been made commercially available. We believe this to be due to the inefficiency of the Boyle synthesis method. In the reported synthesis, the inefficiency of both the formation of the benzofuran backbone, and the benzoylation of the aforementioned product led to low overall yields. Since the original report of BRL-37959, only one other synthetic method has appeared, however it is also plagued with very low yields [3]. In this article, we will present a general procedure to the synthesis of racemic BRL-37959 and several of its analogs in few steps with very good yields, while also studying the benzoylation of 2,3-dihydro-3-methoxycarbonyl benzofurans (**3**) to 7-benzoyl-2,3-dihydro-3-methoxycarbonyl benzofurans (**4**) by bismuth(III) trifluoromethanesulfonate.

The synthesis involves a four-step transformation, ending in the 7-benzoyl-2,3-dihydrobenzofuran-3-carboxylic acid from commercially available salicylaldehydes (*Scheme 1*). 3-Methoxycarbonyl benzofurans (**2**) were synthesized from the corresponding salicylaldehyde (**1**) per the method which our lab reported in 2006 [4]. Reduction of **2** was achieved using magnesium powder in methanol to give the desired 2,3-dihydro-3-methoxycarbonyl benzofuran (**3**) [1]. The reduced benzofuran **3** was then benzoylated to give 7-benzoyl-2,3-dihydro-3-methoxycarbonyl benzofuran (**4**), which was subsequently hydrolyzed to give the desired 7-benzoyl-2,3-dihydrobenzofuran-3-carboylic acid (**5**).

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1) These authors have equal contribution to this project

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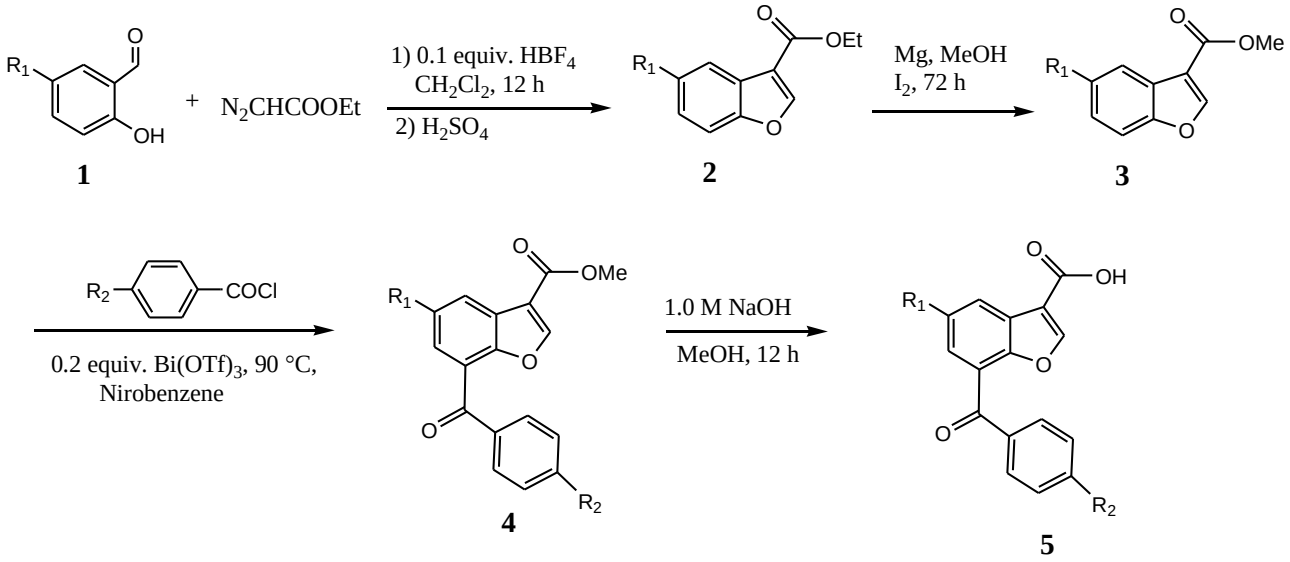
Scheme 1. *The Preparation of BRL-37959 and Analogs from Salicylaldehyde*



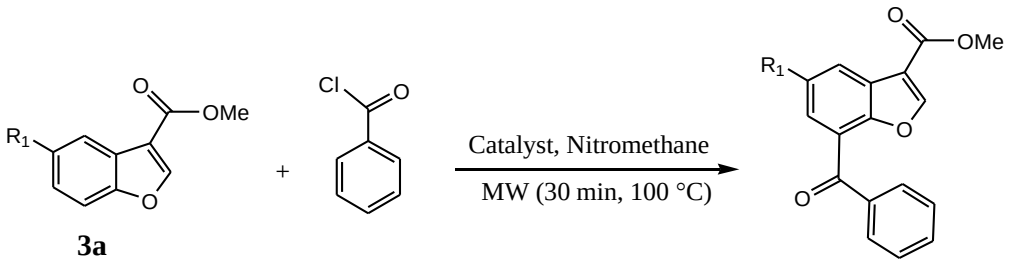
Results and Discussion

To improve the overall yields of final product, we studied and improved the efficacy of the synthetic procedure. The reactions described in *step 1* and *step 2* are reported elsewhere [1,4] and will not be discussed within this article.

Optimization of Benzoylation (step 3) using Microwave. Both previous synthetic procedures reported [1,3] of BRL-37959 required the transesterification of **3** to 2,3-dihydro-3-ethoxycarbonyl benzofuran to achieve the benzoylation of the benzofuran to 7-benzoyl-2,3-dihydro-3-ethoxycarbonyl benzofuran, which would still achieve low yields. Our goal was to achieve the benzoylation of **3** using a microwave reactor, allowing us to bypass one step in the synthesis, while also improving the efficiency and achieving higher yields of benzoylation. We achieved this goal to convert a number of 2,3-dihydro-3-methoxycarbonyl benzofurans to 7-benzoyl-2,3-dihydro-3-methoxycarbonyl benzofurans using $Bi(OTf)_3$ after finding previous reports of this bismuth(III) Lewis acid being effective at catalyzing Friedel-Crafts benzoylations [5]. Initially, we performed the reaction using $AlCl_3$ as the catalyst. However, the 2,3-dihydro-3-methoxycarbonyl benzofurans proved to be sensitive to the $AlCl_3$, resulting in the product being extremely hard to separate leading to only trace yields being recovered. To improve the yield, we investigated the nature and loading of the catalyst, as well as the temperature of the reaction and solvent which the reaction was performed in.

Catalyst screening. Initial attempts of the benzoylation of **5a** were performed using $AlCl_3$ due to it being historically an effective catalyst for benzoylation reactions. Because only trace amounts of product was recovered, we performed the reaction with several other Lewis acid catalysts such as zinc, $AlCl_3$ in the ionic liquid 4,4'-bis[(1,2-dimethylimidazolium)methyl]-2,2'-bipyridine (BIMB), and bismuth(III) trifluoromethanesulfonate [$Bi(OTf)_3$]. The reactions were performed in nitromethane at 100° C for 30 minutes in a microwave reactor. Among these Lewis acids, the $Bi(OTf)_3$ catalyst provided the best yield of 26%. (*Entry 3, Table 1*). Zinc provided low yields, with a significant amount of starting material remaining after the reaction. $AlCl_3$ and the $AlCl_3$ ionic liquid mixture provided only trace yields, with the reaction mixture decomposing making the reaction hard to purify. Increasing loading of the zinc and $AlCl_3$ had negligible effects on the yields.

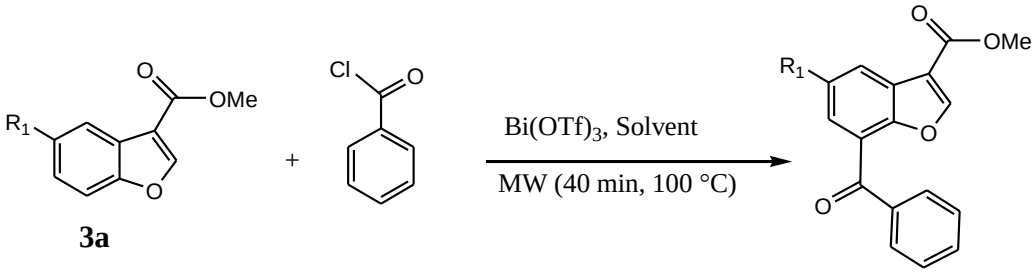
Table 1. *Catalyst Screening*



Entry	Catalyst	Yield of Isolated Product (%)
1	$AlCl_3$	Trace
2	$AlCl_3$ in BIMB	Trace
3	$Bi(OTf)_3$	26
4	Zinc	4

Solvent screening. Once $Bi(OTf)_3$ was chosen as a catalyst, our next effort to improve the yield involved the alteration of solvents to determine the effect of solvent on the yield of benzoylation. From this study, we found that the reaction would proceed neat, but would have trace yields. Low yields were also achieved using dichloromethane. However, when polarity of the solvent was increased to nitromethane, and subsequently nitrobenzene, yields increased significantly. At 100° C, nitrobenzene provided the best results at 62% yield (*Entry 4, Table 2*) however NMR reviled a small amount of reactant decomposition. We believe the more polar solvent helps stabilize the bismuth ions which form, leading to increased reactivity over the course of the reaction.

Table 2. *Solvent Screening*

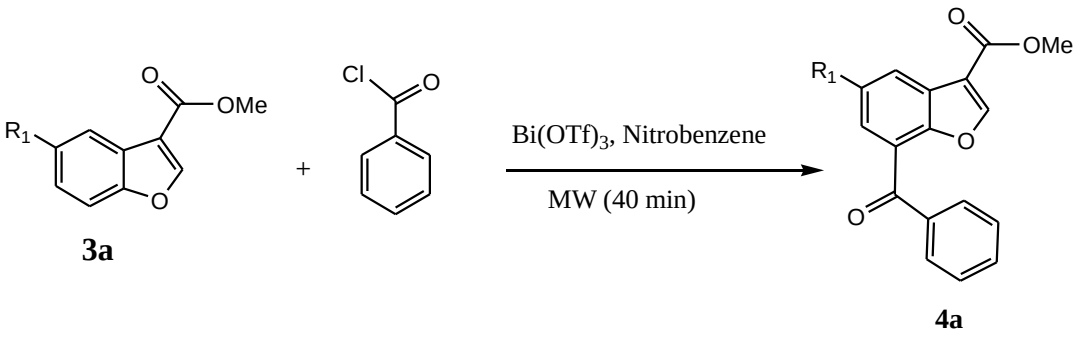


Entry	Solvent	Yield of Isolated Product (%)
1	No Solvent	Trace
2	Nitromethane	26
3	Dichloromethane	2
4	Nitrobenzene	62

Temperature screening. Once nitrobenzene was shown to be the most effective solvent, we chose to determine temperatures effect on the reaction due to nitrobenzene's wider range of effective operation. The results are summarized in *Table 3*. Temperatures were chosen ranging from 70° C to 150° C, with experiments being run at every 10° C interval. At 70° and 80° C reactions were shown to have starting material present. At 90°, 100°, and 110° C all showed minimal amounts of starting material remaining, while product began to have moderate amounts of decomposition at 100° C. All results above 110° C had large amounts of decomposed product, which significantly impeded on the

amount of yield obtained from the reaction. The 90° C was chosen to be the optimal temperature for the reactions, obtaining 68% yield while maintaining minimal amounts of decomposition (*Entry 3, Table 3*).

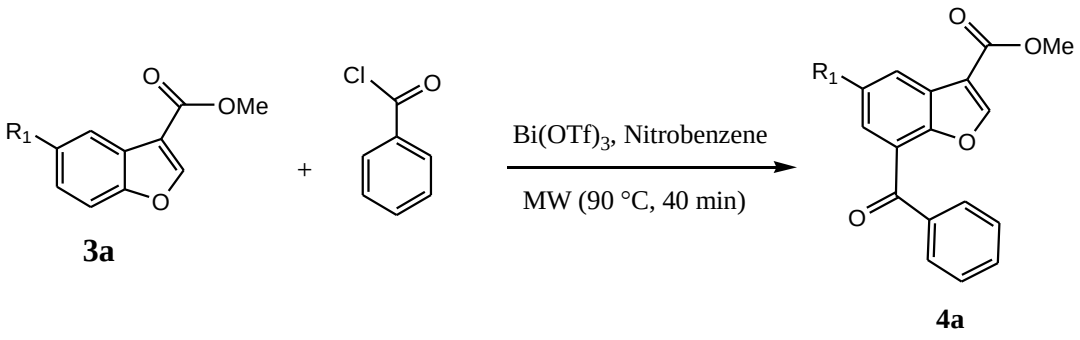
Table 3. *Temperature Screening*



Entry	Temperature (°C)	Yield of Isolated Product
1	70	36
2	80	50
3	90	68
4	100	59
5	110	51

Effect of catalyst loading. Our last effort to improve the yield was performed while altering the amount of catalyst loaded into each reaction. Initially, all reactions were run using 0.1 equiv. of $Bi(OTf)_3$, while subsequent reactions the loading was increased to 0.15, 0.2, and 0.3 equiv. Reaction yields increased significantly up to 0.2 equiv., obtaining a 76% yield, while 0.3 equiv. provided no significant increase in yields over 0.2 equiv. (*Entries 3 and 4, Table 4*).

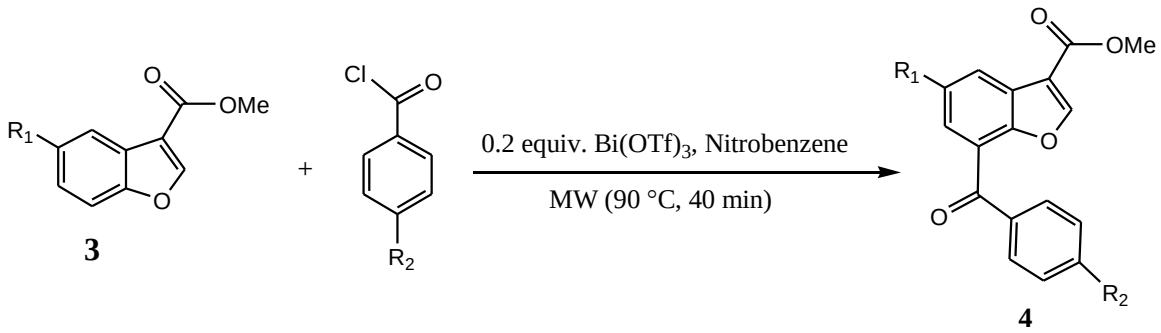
Table 4. *Optimization of the amount of $Bi(OTf)_3$*



Entry	Equiv. of $Bi(OTf)_3$	Yield of Isolated Product (%)
1	0.1	68
2	0.15	71
3	0.2	76
4	0.3	77

Step 3 with optimized reaction conditions. The outcome of our optimization experiments concluded in a significant increase in yield from the initial 26% with $Bi(OTf_3)$ to the final yield of 76%. This optimization suggests that *1*) the choice of catalyst should be $Bi(OTf_3)$; *2)* nitrobenzene should be used as the solvent due to its polar nature; *3)* reactions should be run at 90° C; and *4)* the optimal loading amount of $Bi(OTf_3)$ is 0.2 equiv. Once we obtained these optimal conditions, we performed the reaction with several different substituted benzofuran substrates, as well as several different substituted benzoyl chlorides. The results are presented in *Table 5*.

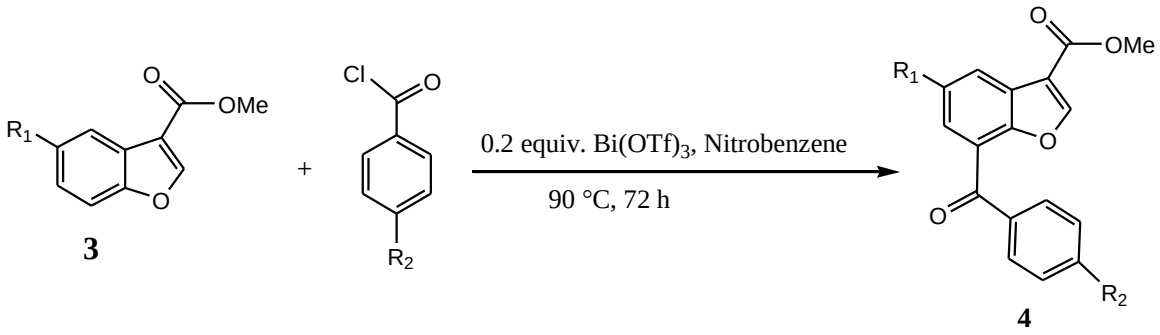
Table 5. *Benzoylation with substituted benzofuran substrates*



Entry	R_1	R_2	Product	Yield of Isolated Product (%)
1	Cl	H	**4a**	77
2	Me	H	**4b**	80
3	F	H	**4c**	51
4	Cl	Cl	**4d**	70
5	Cl	CF_3	**4e**	79
6	Cl	F	**4f**	48

Step 3 reaction under traditional reaction conditions. Realizing that microwave reactions may not be suitable for industrial scale synthesis of the product, we subsequently ran the experiments under traditional reaction conditions. Yields of these reactions (*Table 6*) were shown to be comparable with microwave induced benzoylation reaction (*Table 5*) and they can be easily scaled to larger quantities. In addition, these reactions also showed nearly no decomposition of the starting material or product, indicating that any unreacted starting material could be recycled in future reactions.

Table 6. *Benzoylation with substituted benzofuran substrates under traditional reaction conditions*

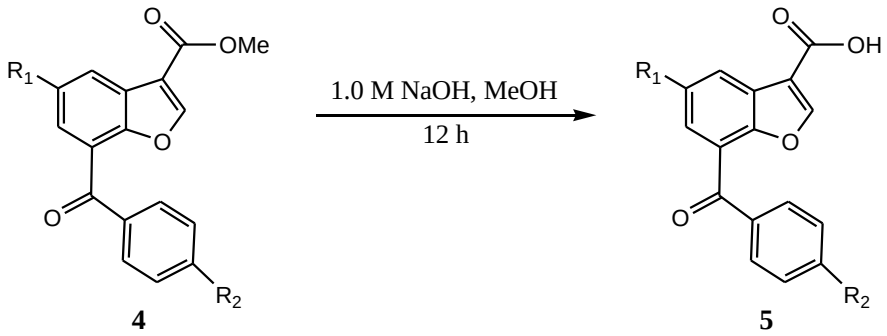


Entry	R_1	R_2	Product	Yield of Isolated Product (%)
1	Cl	H	**4a**	70
2	Me	H	**4b**	77
3	F	H	**4c**	51
4	Cl	Cl	**4d**	62

Hydrolysis of 7-benzoyl-2,3-dihydro-3-methoxycarbonyl benzofuran to 7-benzoyl-2,3-dihydrobenzofuran-3-carboxylic acid. The final step of the synthesis involves the hydrolysis of the methoxy ester to the carboxylic acid. Aqueous 1.0 M NaOH solution was mixed in a 1:1 ratio with

methanol in which the ester was solvated. The solution was allowed to react overnight, after which the reaction was quenched with 6.0 M HCl. The product was isolated by crystallization in water, affording the final product in high yields (*Table 7*).

Table 7. *Hydrolysis Reaction*



4 **5**

Entry	R_1	R_2	Product	Yield of Isolated Product (%)
1	Cl	H	**5a**	95
2	Me	H	**5b**	93
3	F	H	**5c**	95
4	Cl	Cl	**5d**	99
5	Cl	CF_3	**5e**	98
6	Cl	F	**5f**	96

Conclusions

In conclusion, a method of synthesizing the NSAID candidate BRL-37959 has been developed needing only 4 steps from the starting material to the product. This more efficient method allows for the production in high yields, as well as the production of many possible analogs of the compound. The reactions have all been shown to be scalable, indicating a possibility for industrial scale synthesis if the drug shows to be a positive candidate.

Experimental Section

General Considerations

All reactions were performed under a dry N_2 atmosphere in oven dried glassware using standard Schlenk techniques. Flash chromatography was performed using silica gel (SiO_2; 40-140 mesh). HPLC grade CH_2Cl_2 was distilled under N_2 over CaH_2 and introduced into the reaction vessel via a stainless-steel syringe through rubber septa. All NMR data produced using a Bruker DPX300 (300 MHz) instrument. All J coupling values expressed in Hz. The chemical shifts (δ) expressed in ppm relative to tetramethylsilane, using $CDCl_3$ as the solvent. All high-resolution mass spectrometry performed at the Shimadzu Laboratory for Advanced and Applied Analytical Chemistry on a Shimadzu LCMS-IT-TOF. Previously reported compounds were identified by ^1H NMR spectrum. All newly reported compounds were characterized by additional ^{13}C NMR and high resolution mass spectrometry. HPLC analysis was performed using a Waters 1500 series HPLC equipped with a Waters Nova-Pak C18 (3.9 X 300mm) column. All microwave reactions performed in a CEM Discover SP microwave reactor.

General Procedure for the Preparation of 3-Ethoxycarbonyl benzofurans

In a typical experiment, 1.0 equivalence of salicylaldehyde (11.0 – 13.0 mmol) was placed under N_2 in a 3-neck round bottom flask with an addition funnel attached. The salicylaldehyde was dissolved in 10 – 20 mL of freshly distilled CH_2Cl_2. Then 0.1 - 0.2 mmol of $HBF_4{\cdot}OEt_2$ was added to the reaction flask and allowed to stir for 5 minutes. 1.2 equivalence of ethyl diazoacetate (EDA) (14.0 – 16.0 mmol) was added to the

addition funnel and diluted with 10 mL of freshly distilled CH_2Cl_2. The EDA solution was added to the reaction flask dropwise over 1 hour, ensuring the temperature of the reaction never exceeded 36° C. This reaction was allowed to stir overnight, after which it was concentrated *in vacuo*. A 2 mL of concentrated H_2SO_4 was charged to the concentrated mixture and allowed to stir for 30 minutes. The reaction was quenched by adding 5 mL of CH_2Cl_2 and saturated $NaHCO_3$ solution until pH 7. The reaction mixture was washed with water and brine. The products were isolated by flash chromatography (5 – 15% EtOAc in hexane).

5-Chloro-3-ethoxycbonyl benzofuran [1] (**2a**)

From 2.0 g (12.8 mmol) of 5-chlorosalicylaldehyde, 1.74 g (15.3 mmol) of EDA, and 0.11 g (1.3 mmol) of $HBF_4{\cdot}OEt_2$ at room temperature. Yield: 92%. ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.27 (*s*, 1 H, CH); 8.05 (*s*, 1 H, Ph); 7.44 (*d, J=9,* 1 H, Ph); 4.44 (*q, J=7,* 2 H, OCH_2); 1.44 (*t, J=7, 3* H, CH_3).

5-Methyl-3-ethoxycarbonyl benzofuran [1] (**2b**)

From From 1.0 g (7.3 mmol) for 5-methylsalicyladlehyde, 1.0 g (8.8 mmol) of EDA, and 0.12 g (0.73 mmol) of $HBF_4{\cdot}OEt_2$ at room temperature. Yield: 82%. ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.03 (*s*, 1 H, =CH); 7.72 (*s*, 1 H, Ph); 7.19 (*d, J=9*, 1 H, Ph); 6.93 (*d, J=9*, 1 H, Ph); 4.23 (*q, J=7*, 2 H, OCH_2); 2.30 (*s*, 3 H, Ar-CH_3); 1.25 (*t, J=7*, 3 H, CH_3).

5-Fluoro-3-ethoxycarbonyl benzofuran [1] (**2c**)

From 1.0 g (7.1 mmol) of 5-fluorosalicylaldehyde, 0.98 g (8.6 mmol) of EDA, and 0.11 g (1.3 mmol) of $HBF_4{\cdot}OEt_2$ at room temperature. Yield: 74%. ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.28 (s, 1 H, CH); 7.73-7.70 (*m*, 1 H, Ph); 7.48-7.44 (*m*, 1 H, Ph); 7.12-7.06 (*m*, 1 H, Ph); 4.42 (*q, J=7*, 2 H, OCH_2); 1.42 (*t, J=7*, 3 H, CH_3).

General Procedure of the Reduction of 3-Ethoxycarbonyl benzofuran to 2,3-dihydro-3-methoxycarbonyl benzofuran

In a typical experiment, 4.0 – 5.0 mmol (1 equiv) of benzofuran compound was dissolved in 20 – 30 mL of dry MeOH while being stirred vigorously. Once all of the benzofuran is dissolved, 49.4 mol (11.0 equiv) of fresh magnesium powder was added to the reaction vessel, quickly followed by the addition of 0.11 mol (0.1 equiv) of I_2. Reaction was then placed under N_2 atmosphere and allowed to react for 3 days. Reaction progress was monitored by TLC until no starting material remained. After reaction was complete, 25 mL of water added to quench reaction. Magnesium was decomposed by the addition of 6M HCl until no more solid was visible. Product was extracted using CH_2Cl_2 and isolated by flash chromatography (10 – 15% EtOAc in hexane).

5-Chloro-2,3-dihydro-3-methoxycarbonyl benzofuran [1] (**3a**)

From 1.0 g (4.7 mmol) of 5-chloro-3-ethoxycarbonyl benzofuran, 1.2 g (52.1 mmol) of magnesium powder, 0.12 g (0.47 mmol) of iodine at room temperature. Yield: 99%. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.35 (*s*, 1 H, Ph); 7.14 (*dd, J=9, 2*, 1 H, Ph); 6.74 (*d, J=8*, 1 H, Ph); 4.96 (*dd, J=9, 8*, 1 H, CH_2); 4.70 (*t, J=9*, 1 H, CH); 4.34 (*dd, J=9, 8,* 1 H, CH_2); 3.81 (*s*, 3 H, OCH_3).

5-Methyl-2,3-dihydro-3-methoxycarbonyl benzofuran [1] (**3b**)

From 1.0 g (5.6 mmol) of 5-methyl-3-ethoxycarbonyl benzofuran, 1.5 g (62.2 mmol) of magnesium powder, and 0.14 g (0.56 mmol) of iodine at room temperature. Yield: 91%. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.20 (*s*, 1 H, Ph); 7.02 (*d, J=9*, 1 H, Ph); 6.73 (*d, J=9*, 1 H, Ph); 4.92 (*dd, J=9, 7,* 1 H, CH_2); 4.66 (*t, J=9*, 1 H, CH); 4.30 (*dd, J=9, 7*, 1 H, CH_2); 3.80 (*s*, 3 H, Ar-CH_3); 2.32 (*s*, 3 H, OCH_3).

5-Fluoro-2,3-dihydro-3-methoxycarbonyl benzofuran [1] (**3c**)

From 1.0 g (5.1 mmol) of 4-fluoro-3-ethoxycarbonyl benzofuran, 1.4 g (56.5 mmol) of magnesium powder, and 0.13 g (0.51 mmol) of iodine at room temperature. Yield: 82%. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.10 (*d, J=9,* 1 H, Ph); 6.98 (*t, J=9,* 1 H, Ph); 6.87-6.71 (*m,* 1 H, Ph); 4.93 (*dd, J=9, 7, 1* H, CH_2); 4.68 (t, J=9, 1 H, CH); 4.32 (*dd, J=9, 7,* 1 H, CH_2); 3.78 (*s,* 3 H, OCH_3).

General Procedure for the Preparation of 7-Benzoyl-2,3-dihydro-3-methoxycarbonyl benzofuran Using Microwave Reactor

In a typical experiment, 0.04 – 0.06 mmol (0.1 equiv) of $Bi(OTf)_3$ was placed into a 10 mL pressurized microwave reaction vessel. Then, 0.8 -1.2 mmol (2.0 equiv) of benzoyl chloride was charged to the reaction vessel and was allowed to stir. 0.4 – 0.6 mmol (1.0 equiv) of dihydro benzofuran was added to the reaction vessel using 1.5 mL of nitrobenzene, quickly followed by flushing the reaction vessel with N_2 and sealed with a high-pressure Teflon cap. The reaction vessel was placed in the microwave and allowed to react for the allotted reaction time at the reported temperature. All microwave reactions were performed with high stirring, 40 PSI and at 250-watt power. The reaction was quenched with 10 mL of water and extracted with CH_2Cl_2. The organic layer was washed with concentrated $NaHCO_3$ solution and brine. Nitrobenzene was removed by running the product through a thick pad of silica with hexane, causing the product to get stuck in the silica, followed by flushing the silica with CH_2Cl_2 to retrieve the product. The products were isolated by flash chromatography (5 – 20% CH_2Cl_2 in hexane).

7-Benzoyl-5-chloro-2,3-dihydro-3-methoxycarbonyl benzofuran [1] (**4a**)

From 0.10 g (0.47 mmol) of 5-chloro-2,3-dihydro-3-methoxycarbonyl benzofuran, 0.13 g (0.94 mmol) of benzoyl chloride, and 0.03 g (0.047 mmol) of bismuth(III) trifluoromethanesulfonate. Yield: 77%. ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.82 (*d, J=5,* 2 H, Ph); 7.63-7.60 (*m,* 1 H, Ph); 7.53 (*s,* 1 H, Ph); 7.48 (*t, J=10,* 2 H, Ph); 7.44 (*s,* 1 H, Ph); 4.99 (*dd, J=10, 5,* 1 H, OCH); 4.76 (t, *J=10,* 1 H, CH); 4.40 (*dd, 10, 5,* 1 H, OCH); 3.84 (*s,* 3 H, OCH_3). HR-MS: 317.0571 ([*M* + H] $^+$, $C_{17}H_{13}O_4Cl$; calc. 317.0575).

7-Benzoyl-5-methyl-2,3-dihydro-3-methoxycarbonyl benzofuran [1] (**4b**)

From 0.10 g (0.52 mmol) of 5-methyl-2,3-dihydro-3-methoxycarbonyl benzofuran, 0.15 g (1.04 mmol) of benzoyl chloride, and 0.03 g (0.052 mmol) of bismuth(III) trifluoromethanesulfonate. Yield: 80%. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.81 (*d, J=6,* 2 H, Ph); 7.56 (*t, J=6,* 1 H, Ph); 7.45 (*t, J=9,* 2 H, Ph); 7.38 (*s,* 1 H, Ph); 7.25 (*s,* 1 H, Ph); 4.91 (*dd, J=9, 7,* 1 H, OCH); 4.69 (*t, J=9,* 1 H, CH); 4.34 (*dd, J=9, 7,* 1 H, OCH); 3.81 (*s,* 3 H, OCH_3); 2.33 (*s,* 3 H, Ph-CH_3). ^{13}C-NMR ($CDCl_3$, 125 MHz): 20.66; 46.59; 52.74; 73.38; 121.18; 126.05; 128.26; 129.80; 129.90; 130.04; 131.0; 132.70; 137.86; 156.70; 121.28; 194.44. HR-MS: 296.1040 ([*M*]$^+$, $C_{18}H_{16}O_4$; calc. 296.1043).

7-Benzoyl-5-fluoro-2,3-dihydro-3-methoxycarbonyl benzofuran [1] (**4c**)

From 0.10 g (0.51 mmol) of 5-fluoro-2,3-dihydro-3-methoxycarbonyl benzofuran, 0.14 g (1.02 mmol) of benzoyl chloride, and 0.033 g (0.050 mmol) of bismuth(III) trifluoromethanesulfonate. Yield: 51%. ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.82 (*d, J=10,* 2 H, Ph); 7.61 (*t, J=7,* 2 H, Ph); 7.49 (*t, J=15,* 2 H, Ph); 7.45 (*s,* 1 H, Ph); 4.97 (*dd, J=10,* 5, 1 H, OCH), 4.75 (*t, J=10,* 1 H, CH); 4.44 (*dd, J=10,* 5, 1 H, OCH); 3.86 (*s,* 3 H, OCH_3).

5-Chloro-7-(4-chlorobenzoyl)-2,3-dihydro-3-methoxycarbonyl benzofuran (**4d**)

From 0.10 g (0.47 mmol) of 5-chloro-2,3-dihydro-3-methoxycarbonyl benzofuran, 0.17 g (0.94 mmol) of 4-chlorobenzoyl chloride and 0.06 g (0.092 mmol) of bismuth(III) trifluoromethanesulfonate. Yield : 70 %. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.77 (*d, J=9,* 2 H, Ph); 7.55 (*s,* 1 H, Ph); 7.47-7.44 (*m,* 3 H, Ph); 4.98 (*dd, J=9, 6,* 1 H, OCH); 4.74 (*t, J=9,* 1 H, CH); 4.39 (*dd, J=9, 6,* 1 H, OCH); 3.85 (*s,* 3 H, OCH_3).

5-Chloro-7-(4-(trifluoromethyl)benzoyl)-2,3-dihydro-3-methoxycarbonyl benzofuran- (**4e**)

From 0.10 g (0.47 mmol) of 5-chloro-2,3-dihydro-3-methoxycarbonyl benzofuran, 0.20 g (0.94 mmol) of 4-(trifluromethyl)benzoyl chloride and 0.06 g (0.092 mmol) of bismuth(III) trifluoromethanesulfonate. Yield : 79 %. ^{1}H-NMR ($CDCl_3$, 500 MHz): 8.02 (*d,* J=5, 1H, Ph); 7.91 (*d, J=5,* 1H, Ph); 7.80-7.75 (*m,* 2 H, Ph); 7.48-7.33 (*m,* 2 H, Ph); 4.99 (*dd, J=10, 5,* 1 H, OCH); 4.76 (*dd, J=10, 5,* 1 H, CH); 4.45 (*dd, J=10, 5,* 1 H, OCH). HR-MS: 371.0290 ([*M* + H]$^+$, $C_{17}H_{10}O_4F_3Cl$; calc. 371.0292).

5-Chloro-7-(4-fluorobenzoyl)-2,3-dihydro-3-methoxycarbonyl benzofuran (**4f**)

From 0.10 g (0.47 mmol) of 5-chloro-2,3-dihydro-3-methoxycarbonyl benzofuran, 0.15 g (0.94 mmol) of 4-fluorobenzoyl chloride and 0.06 g (0.092 mmol) of bismuth(III) trifluoromethanesulfonate. Yield: 48%. ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.78 (*d, J=10,* 2 H, Ph); 7.62 (*s,* 1 H, Ph); 7.49-7.46 (*m*, 3 H, Ph); 4.98 (*dd*, J=10, 5, 1 H, OCH); 4.76 (*t, J=10*, 1 H, CH); 4.46 (*dd*, *J=10*, 5, 1 H, OCH). HR-MS: 320.0244 ([*M*]$^+$, $C_{16}H_{10}O_4FCl$; calc. 320.0246).

General procedure for the Preparation of 7-Benzoyl-2,3-dihydro-3-methoxycarbonyl bezofurans

In a typical experiment, 0.1 equiv. (0.04 – 0.06 mmol) of $Bi(OTf)_3$ was charged to a reaction vessel equipped with a reflux condenser and placed under N_2. Then, 0.8 – 1.2 mmol (2.0 equiv.) of benzoyl chloride was charged to the reaction vessel and allowed to stir for 10 minutes. 1 equiv. of reduced benzofuran (0.4 – 0.6 mmol) was then diluted in 1.5 – 3.0 mL of nitrobenzene and charged to the reaction vessel using a stainless-steel syringe. The reaction was then brought to temperature and allowed to stir for up to 3 days. The reaction was then quenched with 10 mL of water, and washed with $NaHCO_3$ and brine. The nitrobenzene was removed by running the product through a silica plug in hexane, causing the product to stick in the silica, and subsequent CH_2Cl_2 flush once all nitrobenzene is removed. The products were then isolated by flash chromatography (5 – 20% $CHCl_2$ in hexane).

7-Benzoyl-5-chloro-2,3-dihydro-3-methoxycarbonyl bezofuran [1] (**4a**)

From 0.50 g (2.35 mmol) of 5-chloro-2,3-dihydro-3-methoxycarbonyl benzofuran, 0.66 g (4.70 mmol) of benzoyl chloride, and 0.15 g (0.235 mmol) of $Bi(OTf_3)$ at 90 °C. Yield: 70%.

7-Benzoyl-5-methyl-2,3-dihydro-3-methoxycarbonyl benzofuran [1] (**4b**)

From 0.50 g (2.60 mmol) of 5-methyl-2,3-dihydro-3-methoxycarbonyl benzofuran, 0.73 g (5.20 mmol) of benzoyl chloride, and 0.17 g (0.26 mmol) of bismuth(III) trifluoromethanesulfonate at 90 °C. Yield: 77%.

7-Benzoyl-5-fluoro-2,3-dihydro-3-methoxycarbonyl benzofuran [1] (**4c**)

From 0.10 g (0.51 mmol) of 5-fluoro-2,3-dihydro-3-methoxycarbonyl benzofuran, 0.14 g (1.02 mmol) of benzoyl chloride, and 0.033 g (0.050 mmol) of bismuth(III) trifluoromethanesulfonate at 90 °C. Yield: 51%.

5-Chloro-7-(4-chlorobenzoyl)-2,3-dihydro-3-methoxycarbonyl benzofuran (**4d**)

From 0.50 g (2.35 mmol) of 5-chloro-2,3-dihydro-3-methoxycarbonyl benzofuran, 0.82 g (4.70 mmol) of 4-chlorobenzoyl chloride, and 0.15 g (0.235 mmol) of bismuth(III) trifluoromethanesulfonate at 90 °C. Yield: 62%.

General Procedure for the Saponification of 7-Benzoyl-2,3-dihydro-3-methoxycarbonyl benzofuran to 7-Benzoyl-2,3-dihydrobenzofuran-3-carboxylic acid

In a typical experiment, 0.08 – 0.12 mmol (1.0 equiv) of benzofuran starting material was dissolved in 10 mL of MeOH. Then, 10 mL of 1M NaOH solution was charged to the flask and allowed to stir overnight. In the morning, reaction was monitored by TLC to ensure completion, and subsequently quenched with 3 mL of 6M HCl. Product was isolated by crystallization in 10 mL of water.

7-Benzoyl-5-chloro-2,3-dihydrobenzofuran-3-carboxylic acid [1] (**5a**)

From 0.05 g (0.158 mmol) of 7-benzoyl-5-chloro-2,3-dihydro-3-methoxycarbonyl benzofuran. Yield: 95%. ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.83 (*d, J=5,* 2 H, Ph); 7.62 (*t, J=5,* 1 H, Ph); 7.51 *(t, J=5,* 2 H, Ph); 7.49 (*s,* 1 H, Ph); 7.47 (*s,* 1 H, Ph); 5.00 (*dd, J=10, 5,* 1 H, OCH); 4.78 (*t, J=10,* 1 H, CH); 4.46 (*dd, J=10, 5,* 1 H, CH). ^{13}C-NMR ($CDCl_3$, 125 MHz): 30.94; 46.23; 73.52; 122.34; 125.66; 127.38; 128.43; 129.15; 129.91; 130.52; 133.28; 137.03; 157.25; 167.30; 192.99. HR-MS: 303.0416 ([*M* + H]$^+$, $C_{16}H_{11}O_4Cl$; calc. 303.0419).

7-Benzoyl-5-methyl-2,3-dihydrobenzofuran-3-carboxylic acid [1] (**5b**)

From 0.07 g (0.236 mmol) of 7-benzoyl-5-methyl-2,3-dihydro-3-methoxycarbonyl benzofuran. Yield: 93% ^{1}H-NMR (CD_3OD, 300 MHz): 7.78 (*d, J=3,* 2 H, Ph); 7.62 (*t, J=3,* 1 H, Ph); 7.51-7.48 (*m,* 2 H, Ph); 7.48 (*s,* 1 H, Ph); 7.21 (*s,* 1 H, Ph); 4.86 (*dd, J=6,* 3, 1 H, OCH); 4.65 (*t, J= 6,* 1 H, CH); 4.38 (*dd, J=6, 3,* 1 H, OCH); 2.35 (*s,* 3 H, $PhCH_3$). ^{13}C-NMR ($CDCl_3$, 125 MHz): 20.65; 46.42; 73.11; 121.22; 125.48; 128.22; 129.82; 129.92; 130.25; 121.24; 132.77; 137.79; 156.70; 175.67; 194.47. HR-MS: 282.0890 ($[M]^+$, $C_{17}H_{14}O_4$; calc. 282.0887).

7-Benzoyl-5-fluoro-2,3-dihydrobenzofuran-3-carboxylic acid [1] (**5c**)

From 0.05 g (0.167 mmol) of 7-benzoyl-5-fluoro-2,3-dihydro-3-methoxycarbonyl benzofuran. Yield: 95%. ^{1}H-NMR ($CDCl_3$, 500 MHz): 11.40-10.88 (*s,* 1 H, COOH); 7.82 (*d, J=10,* 2 H, Ph); 7.63-7.60 (*m,* 2 H, Ph), 7.49-7.45 (*m,* 3 H, Ph); 4.97 (*dd, J=10, 5,* 1 H, OCH); 4.75 (*t, J=10,* 1 H, CH); 4.44 (*t, J=10,* 1 H, OCH). HR-MS: 286.0635 ($[M]^+$, $C_{16}H_{11}O_4F$; calc. 286.0636).

5-Chloro-7-(4-chlorobenozyl)-2,3-dihydrobenzofuran-3-carboxylic acid [1] (**5d**)

From 0.03 g (0.085 mmol) of 5-chloro-7-(4-chlorobenzoyl)-2,3-dihydro-3-methoxycarbonyl benzofuran. Yield: 99%. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.75 (*d, J=5,* 2 H, Ph); 7.61 (*s,* 1 H Ph); 7.45-7.42 (*m,* 3H, Ph); 4.96 (*t, J=10,* 1 H, OCH); 4.73 (*t, J=10,* 1 H, CH); 4.40 (*t, J=10,* 1 H, OCH). ^{13}C-NMR ($CDCl_3$, 125 MHz): 29.70; 46.00; 73.59; 121.99; 125.91; 127.45; 128.78; 129.37; 130.37; 131.23; 135.59; 153.21; 164.62; 192.79; HR-MS: 335.9955 ($[M]^+$, $C_{16}H_{10}O_4Cl_2$; calc. 335.9951).

5-Chloro-7-(4-(trifluoromethyl)benzoyl)-2,3-dihydrobenzofuran-3-carboxylic acid (**5e**)

From 0.04 g (0.104 mmol) of 5-chloro-7-(4-(trifluoromethyl)benzoyl)-2,3-dihydro-3-methoxycarbonyl benzofuran. Yield: 98%. ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.76 (*d, J=5,* 2 H, Ph); 7.62 (*s,* 1 H, Ph); 7.48-7.47 (*m,* 3 H, Ph); 4.99 (*dd, J=10, 5,* 1 H, OCH); 4.76 (*t, J=10,* 1 H, CH); 4.45 (*dd, J=10, 5,* 1 H, OCH). HR-MS: 371.0290 ($[M + H]^+$, $C_{17}H_{10}O_4F_3Cl$; calc. 371.0292).

5-Chloro-7-(4-fluorobenzoyl)-2,3-dihydrobenzofuran-3-carboxylic acid. (**5f**)

From 0.05 g (0.150 mmol) of 5-chloro-7-(4-fluorobenzoyl)-2,3-dihydro-3-methoxycarbonyl benzofuran. Yield: 96%. ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.78 (*d, J=10,* 2 H, Ph); 7.62 (*s,* 1 H, Ph); 7.50-7.45 (*m,* 3 H, Ph); 4.98 (*dd,* J=10, 5, 1 H, OCH); 4.76 (*t, J=10,* 1 H, CH); 4.44 (*t, J=10,* 1 H, OCH). HR-MS: 320.0244 ($[M]^+$, $C_{16}H_{10}O_4FCl$; calc. 320.0246).

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Author Contribution Statement

Synthesis: Shamsul A. Ahmed, Damon J. Hinz and Marcus J. Jellen. Design the synthesis: *Damon J. Hinz, Shamsul A. Ahmed, and M. Mahmun Hossain.* Wrote the paper: *Damon J. Hinz, Shamsul A. Ahmed and M Mahmun Hossain*

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