Regioselective Synthesis of Benzofuranones and Benzofurans

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ABSTRACT: Reaction of 3-hydroxy-2-pyrones with nitroalkenes bearing ester groups gives benzofuranones. The reaction allows regioselective preparation of the benzofuranones with programmable substitution at any position. Complex substitution patterns are readily created. The substituted benzofuranones can be converted to substituted benzofurans.

Benzofuranones, benzofurans, and related functional groups appear as substructures in natural products, pharmaceuticals, biologically active food chemicals, and illicit psychoactive compounds. For example, amiodarone (1) is a benzofuran that is a commonly prescribed medicine for cardiac arrhythmias (Figure 1). Fumimycin (2) is a benzofuranone natural product that displays antibiotic activity by inhibiting the bacterial protein deformylase enzyme. Bergamottin (3) is a cytochrome P450 inhibitor found in citrus fruits, and it is implicated in grapefruit−drug interactions. Finally, 2C-B-FLY (4) is a dihydrobenzofuran biosisostere of mescaline, which was prepared for SAR investigation of the serotonin receptors, and it has been used as a recreational hallucinogen.

The importance of biologically active benzofuran derivatives has fueled decades of research into their chemical synthesis. A classical and common strategy for their synthesis is shown in Scheme 1. An α-phenoxy carbonyl compound undergoes cyclization (e.g., intramolecular Friedel−Crafts-type condensation) to build the five-membered furanoid ring. This strategy exemplifies issues of regiochemical control in the formation of benzofurans and derivatives, in that it is particularly useful when the regiochemical outcome of the reaction is predictable. For example, substrate 5 has only one ortho site available for cyclization, and the product (6) is formed as a single regioisomer. When both ortho positions are unsubstituted, the sterically less-hindered product is commonly favored. For example, cyclization of 7 leads to 3,6-disubstituted benzofuran 8, and the 3,4-disubstituted congener 9 is not observed. In cases where steric considerations do not provide a strong preference, regiochemical mixtures are common. Cyclization of 10 leads to a mixture of 11 and 12 in a ratio of 53:37, respectively.

We recently discovered a new synthesis of substituted phenols from 3-hydroxy-2-pyrones (13) and nitroalkenes (14, Scheme 2). The reaction allows for high levels of substitution, including even hexasubstituted benzenes, and very good regioselectivity (tr = ~200:1). Mechanistically, a Diels−Alder cycloaddition of 13 and 14 gives 15. Elimination...
Scheme 2. Diels–Alder Based Phenol and Benzofuranone Syntheses

![Scheme 2](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>T (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1**</td>
<td>AlCl₃ (10 mol %)</td>
<td>150</td>
<td>2</td>
<td>53 (23) + 15 (24)</td>
</tr>
<tr>
<td>2</td>
<td>AlCl₃ (10 mol %)</td>
<td>150</td>
<td>24</td>
<td>45</td>
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<tr>
<td>3</td>
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</tr>
<tr>
<td>4</td>
<td>AlCl₃ (10 mol %), TFA (20 mol %)</td>
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<td>24</td>
<td>58</td>
</tr>
<tr>
<td>5</td>
<td>i. AlCl₃ (10 mol %); ii. TFA (20 mol %)</td>
<td>120</td>
<td>20</td>
<td>53</td>
</tr>
<tr>
<td>6</td>
<td>AlCl₃ (10 mol %), TFA (20 mol %)</td>
<td>120</td>
<td>20</td>
<td>64</td>
</tr>
<tr>
<td>7</td>
<td>Pb(OH)₂ (10 mol %), TFA (20 mol %)</td>
<td>120</td>
<td>6</td>
<td>55</td>
</tr>
<tr>
<td>8</td>
<td>BF₃OEt₂ (10 mol %)</td>
<td>120</td>
<td>6</td>
<td>52</td>
</tr>
<tr>
<td>9</td>
<td>Me₂AlCl (10 mol %), TFA (20 mol %)</td>
<td>100</td>
<td>2.5</td>
<td>29 (23) + 30 (24)</td>
</tr>
<tr>
<td>10</td>
<td>AlCl₃ (10 mol %), pTsOH (20 mol %)</td>
<td>120</td>
<td>6</td>
<td>33</td>
</tr>
<tr>
<td>11</td>
<td>AlCl₃ (10 mol %), HCl (1 equiv)</td>
<td>150</td>
<td>1.5</td>
<td>32</td>
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<tr>
<td>12</td>
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<td>3</td>
<td>35</td>
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<tr>
<td>13</td>
<td>AlCl₃ (10 mol %), pTsOH (20 mol %), 4 Å MS</td>
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<td>27</td>
<td>19</td>
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<tr>
<td>14**</td>
<td>AlCl₃ (10 mol %), TFA (20 mol %)</td>
<td>120</td>
<td>20</td>
<td>64</td>
</tr>
</tbody>
</table>

**Isolated % yield of 24, unless otherwise noted. *o-DCB (0.5 M). BuCN (0.3 M) was used as the solvent.

Note: In an attempt to sequester the methanol byproduct gave a substantially decreased yield (entry 13). Finally, different solvents were evaluated but did not change the chemical yield of the reaction (entry 14).

The benzofuranone synthesis was then evaluated with other substrate combinations to explore the tolerance of the reaction to substitution (Scheme 3). A variety of 4-substituted-3-hydroxy-2-pyrones (13, R¹ ≠ H) were efficiently converted to substituted benzofuranones 20. Methyl (25), branched alkyl (26), and phenyl groups (27) were all well tolerated. Pyrones in an attempt to sequester the methanol byproduct gave a substantially decreased yield (entry 13). Finally, different solvents were evaluated but did not change the chemical yield of the reaction (entry 14).

The benzofuranone synthesis was then evaluated with other substrate combinations to explore the tolerance of the reaction to substitution (Scheme 3). A variety of 4-substituted-3-hydroxy-2-pyrones (13, R¹ ≠ H) were efficiently converted to substituted benzofuranones 20. Methyl (25), branched alkyl (26), and phenyl groups (27) were all well tolerated. Pyrones

![Scheme 3](image)
with multiple substitution also participated in the reaction. 5,6-Disubstituted benzofuran 28 was prepared in moderate yield; however, note that this type of benzofuran is difficult to prepare as a single regioisomer using standard condensation conditions. Trisubstituted benzofuranones 29, 30, and 31 were all prepared in synthetically useful yields. Finally, 4,7-disubstituted benzofurans bearing methyl groups (32), different alkyl groups (33), and electron-withdrawing groups (34) were also prepared using our method.

An advantage of preparing benzofuranones is that they are conveniently transformed into substituted benzofurans. For example, 34 can be olefination under standard Wittig conditions to give 2,4,7-trisubstituted benzofuran 35 (Scheme 4).16 Benzofuran 34 can also be converted to the corresponding triflate 36.17 Triflate 36 can be reduced to the parent benzofuran 37.18 Alternatively, triflate 36 can undergo Sonogashira coupling to give 2-alkynyl benzofuran 38.19 Suzuki–Miyaura coupling of 36 gives the corresponding 2-aryl benzofuran 39.20

In summary, we have created a new benzofuranone synthesis from substituted 3-hydroxypyrones and nitroalkenes. The reaction tolerates a variety of substitution patterns, and it gives synthetically useful yields. The reaction is completely regioselective: the regioisomer of the product is completely predictable through inspection of the starting material substitution, and no issues of regiochemical mixtures are observed. Finally, the benzofuranone products are conveniently converted into the corresponding substituted benzofurans.

### EXPERIMENTAL SECTION

**General Experimental Details.** All reactions were carried out under an inert Ar atmosphere in oven-dried glassware. External (heated oil or cryogenic solvent) bath temperatures were used to record all reaction temperatures. Flash column chromatography (FCC) was carried out with SiliaFlash P60, 60 Å silica gel. Reactions and column chromatography were monitored with EMD silica gel 60 F254 plates and visualized with potassium permanganate stain. Reagent grade 1,4-dioxane was dried over CaH₂ and distilled prior to use. 1,2-Dichlorobenzene (DCB) was distilled under reduced pressure and degassed using three freeze–pump–thaw cycles. Tetrahydrofuran (THF), toluene, and benzene were dried by passage through activated alumina columns. All other reagents and solvents were used without further purification from commercial sources. Unless otherwise noted, melting points were obtained from material that solidified after chromatography.

**Instrumentation:** FT-IR spectra were obtained on NaCl plates with a PerkinElmer Spectrum Vision spectrometer. HRMS were recorded on a JEOL MS Route Magnetic Sector Instrument (EI) or a Waters Synapt HDMS TOF instrument (ESI). Proton and carbon NMR spectra (1H NMR and 13C NMR) were recorded in deuterated chloroform (CDCl₃) unless otherwise noted on a Bruker 700 MHz Avance III Spectrometer with carbon-optimized cryoprobe or Bruker 400 MHz DPX-400 spectrometer. Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Melting points were determined with a Cole-Parmer instrument and are uncorrected.

**General Procedure for Benzofuranone Syntheses.** To a thick-walled reaction vessel were added the pyrone (0.2 mmol, 2 equiv), nitroalkene (0.1 mmol, 1 equiv), BHT (0.01 mmol, 0.1 equiv), and AlCl₃ (0.01 mmol, 0.1 equiv). The vessel was flushed with Ar gas for 5 min. DCB (0.2 mL, 0.5 M) and TFA (0.02 mmol, 0.2 equiv) were added, and the tube was quickly sealed. The reaction mixture was heated to 120 °C for 16 h unless otherwise noted. The reaction mixture was cooled to rt, and the mixture was directly purified by FCC without aqueous workup.

**Benzofuran-2(3H)-one (24).** 3-Hydroxy-2H-pyran-2-one (44.8 mg, 0.4 mmol) and methyl 3-nitrobut-3-enoate (29 mg, 0.2 mmol) were subjected to the general procedure for 20 h. Purification by FCC (20:1 hexanes/EtOAc) yielded 24 as a solid (173 mg, 58%).

**7-Isobutylbenzofuran-2(3H)-one (27).** 3-Hydroxy-4-isobutyl-2H-pyran-2-one (50.4 mg, 0.4 mmol) and methyl 3-nitrobut-3-enoate (29 mg, 0.2 mmol) were subjected to the general procedure for 8 h. Purification by FCC (20:1 hexanes/EtOAc) yielded 27 as a solid (137 mg, 58%).

**Scheme 4. Synthesis of Substituted Benzofurans**

![Scheme 4](https://doi.org/10.1021/acs.joc.1c00341)
Methyl 7-Methyl-2-oxo-2,3-dihydrobenzofuran-4-carboxylate (34). 3-Hydroxy-4-methyl-2H-pyran-2-one (38 mg, 0.30 mmol) and dimethyl-3-nitropent-3-enoate (30.5 mg, 0.15 mmol) were subjected to the general procedure at 150 °C for 2 h. Purification by FCC (20:1 hexanes/EtOAc) yielded 34 as a solid (131 mg, 42%). Data for 34: Rf 0.43 (5:1 hexanes/EtOAc); mp: 123-124 °C. IR (thin film) 2956, 1804, 1706, 1304 cm⁻¹; 1H NMR (700 MHz, CDCl₃) δ 7.70 (d, J = 7.7 Hz, 1 H), 7.21 (d, J = 7.7 Hz, 1 H), 4.04 (s, 2 H), 3.92 (s, 3 H), 2.37 (s, 3 H); 31C(H) NMR (176 MHz, CDCl₃) δ 174.1, 165.9, 153.5, 130.2, 126.3, 125.2, 124.8, 124.2, 52.3, 35.0, 15.6; HRMS (ESI) m/z: [M + H⁺]⁺ Calcd for C₁₅H₁₄O₄ 281.0705; Found 281.0677.

Methyl 2-(2-Methoxy-2-oxoethyl)-7-methylbenzofuran-4-carboxylate (35). To a solution of methyl 7-methyl-2-oxo-2,3-dihydrobenzofuran-4-carboxylate (20.6 mg, 0.1 mmol, 1 equiv), methyl (triethyl phosphoranylidene) acetate (50.1 mg, 0.15 mmol, 1.5 equiv) and toluene (0.5 mL, 0.2 M). The vessel was flushed with Ar gas for 1 min and then quickly sealed. The reaction mixture was heated to 100 °C for 1 h. A reaction mixture was cooled to rt, and the mixture was directly purified by FCC (16:1 hexanes/CH₂Cl₂/EtOAc) without aqueous workup to yield 35 as a solid (17.6 mg, 67%). Data for 35: Rf 0.375 (1:1 hexanes/EtOAc); mp: 77-80 °C. IR: (thin film) 2955, 1745, 1714, 1599, 1435, 1266, 1198 cm⁻¹; 1H NMR (700 MHz, CDCl₃) δ 7.86 (d, J = 7.7 Hz, 1 H), 7.22 (s, 1 H), 7.11 (d, J = 7.7 Hz, 1 H), 3.95 (s, 3 H), 3.89 (s, 2 H), 3.77 (s, 3 H), 2.55 (s, 3 H); 31C(H) NMR (176 MHz, CDCl₃) δ 169.2, 167.1, 154.2, 152.2, 128.5, 126.8, 125.7, 124.6, 120.9, 110.8, 52.6, 51.9, 34.6, 15.5; HRMS (ESI) m/z: [M + Na⁺]⁺ Calcd for C₁₅H₁₅O₃Na 285.0739; Found 285.0730.

Methyl 7-Methyl-2-((trifluoromethylsulfonyl)oxy)benzofuran-4-carboxylate (36). A solution of methyl 7-methyl-2-oxo-2,3-dihydrobenzofuran-4-carboxylate (108 mg, 0.52 mmol, 1 equiv) in THF (14 mL, 0.038 M) was added LiHMDS (1 M in THF, 1.05 mL, 1 mmol, 2 equiv) at ~78 °C. The mixture was stirred at ~78 °C for 1 h. The mixture was quenched with water (20 mL) and extracted with EtOAc (4 x 30 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. The residue was purified by FCC (40:1 hexanes/EtOAc) to yield 36 as a solid (119 mg, 67%). Data for 36: Rf 0.57 (5:1 hexanes/EtOAc); mp: 39-40 °C. IR: (thin film) 2956, 1722, 1600, 1439, 1230 cm⁻¹; 1H NMR (700 MHz, CDCl₃) δ 7.94 (d, J = 7.7 Hz, 1 H), 7.23 (d, J = 7.7 Hz, 1 H), 7.07 (s, 1 H), 3.97 (s, 3 H), 2.55 (s, 3 H); 31C(H) NMR (176 MHz, CDCl₃) δ 166.3, 150.5, 149.5, 127.4, 127.0, 126.8, 126.1, 121.1, 118.7 (q, J = 318 Hz), 94.7, 52.1, 15.2; HRMS (ESI) m/z: [M + H⁺]⁺ Calcd for C₁₅H₁₄O₃SNaF₃ 291.0153; Found 293.0154.

Methyl 7-Benzofuran-2-carboxylate (37). A solution of methyl 7-methyl-2-(((trifluoromethylsulfonyl)oxy)benzofuran-4-carboxylate (25 mg, 0.075 mmol, 1 equiv) in THF (1.5 mL, 0.05 M) was sparged with Ar gas for 5 min. PdCl₂(dppf) (2.8 mg, 0.00375 mmol, 5 equiv) was added dropwise. The mixture was stirred at rt for 1.5 h. The reaction was quenched with brine (15 mL) and extracted with EtOAc (4 x 30 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. The residue was purified by FCC (40:1 hexanes/EtOAc) to yield 37 as an oil (119 mg, 67%).

Note
https://doi.org/10.1021/acs.joc.1c00341
Methyl 7-Methyl-2-phenylbenzofuran-4-carboxylate (38). To a round-bottom flask was added a solution of methyl 7-methyl-2-(((trifluoromethyl)sulfonyl)oxy)benzofuran-4-carboxylate (25 mg, 0.075 mmol, 1 equiv) in benzene (0.5 mL, 0.15 M). The headspace of the flask was evacuated and backfilled with Ar three times. Phenylecetanyle (15.3 mg, 0.15 mmol, 2 equiv), CuI (2.1 mg, 0.01125 mmol, 15 mol %), diisopropanolamine (30 mg, 0.3 mmol, 4 equiv), and Pd(PPh3)4 (8.7 mg, 0.0075 mmol, 10 mol %) were added under Ar. The mixture was stirred at rt for 1 h. The reaction was quenched with saturated aqueous NH4Cl solution (15 mL) and extracted with EtOAc (4 × 15 mL). The combined organic layers were dried over Na2SO4, filtered, and concentrated. The residue was purified by FCC (40:1 hexanes/EtOAc) to yield 39 as a solid (19.7 mg, 91%). Data for 38: Rf 0.32 (20:1 hexanes/EtOAc); mp: 71–76 °C; IR: (thin film) 2950, 1716, 1270 cm−1; 1H NMR (700 MHz, CDCl3) δ 7.91 (d, J = 7.7 Hz, 1 H), 7.61 (d, J = 6.3 Hz, 2 H), 7.59 (s, 1 H), 7.41–7.40 (m, 3 H), 7.19 (d, J = 7.7 Hz, 1 H), 3.98 (s, 3 H), 2.60 (s, 3 H); 13C{1H} NMR (176 MHz, CDCl3) δ 166.8, 154.1, 140.1, 131.8, 129.4, 128.5, 127.7, 127.0, 126.3, 125.9, 121.7, 120.3, 113.1, 95.7, 79.6, 52.0, 15.5; HRMS (ESI) m/z: [M + H]+ Calcd for C16H16O2; Found: 267.1021. Methyl 7-Methyl-2-phenylbenzofuran-4-carboxylate (39). To a solution of methyl 7-methyl-2-(((trifluoromethyl)sulfonyl)oxy)benzofuran-4-carboxylate (17 mg, 0.05 mmol, 1 equiv) in 1,4-dioxane/water (1:1) (0.5 mL, 0.1 mmol, 0.1 M) was added phenylboronic acid (9.2 mg, 0.075 mmol, 1.5 equiv). The mixture was warmed to rt and stirred for 3 h. Solvent was removed under vacuum. The crude reaction mixture was dissolved in EtOAc, filtered through Celite, dried over Na2SO4, filtered, and concentrated. The residue was purified by GCC (50:1 hexanes/EtOAc) to yield 39 as a solid (6.5 mg, 49%). Data for 39: Rf 0.25 (20:1 hexanes/EtOAc); mp: 58–61 °C; IR: (thin film) 2953, 1714, 1434, 1269, 1200 cm−1; 1H NMR (700 MHz, CDCl3) δ 7.95 (d, J = 7.7 Hz, 2 H), 7.88 (d, J = 7.7 Hz, 1 H), 7.64 (s, 1 H), 7.48 (s, J = 7.7 Hz, 2 H), 7.39 (s, J = 7.7 Hz, 1 H), 7.13 (d, J = 7.7 Hz, 1 H), 4.00 (s, 3 H), 2.64 (s, 3 H); 13C{1H} NMR (176 MHz, CDCl3) δ 167.2, 157.3, 154.0, 130.2, 129.3, 129.0, 128.9, 126.8, 125.8, 125.3, 124.7, 119.9, 102.8, 51.9, 15.5; HRMS (ESI) m/z: [M + H]+ Calcd for C17H16O2; Found: 267.1028.

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**REFERENCES**


