JOC The Journal of Organic Chemistry

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Regioselective Synthesis of Benzofuranones and Benzofurans

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Cite This: J. Org. Chem. 2021, 86, 6931−6936 Read Online

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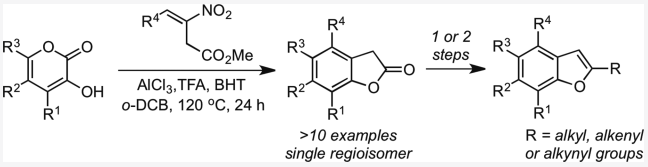
ABSTRACT: Reaction of 3-hydroxy-2-pyrones with nitroalkenes bearing ester groups gives benzofuranones. The reaction allows regioselective preparation of the benzofuranones with programmable substitution at any position. Complex substitution patterns are readily created. The substituted benzofuranones 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.[1] For example, amiodarone (**1**) is a benzofuran that is a commonly prescribed medicine for cardiac arrhythmias (Figure 1).[2] Fumimycin (**2**) is a benzofuranone

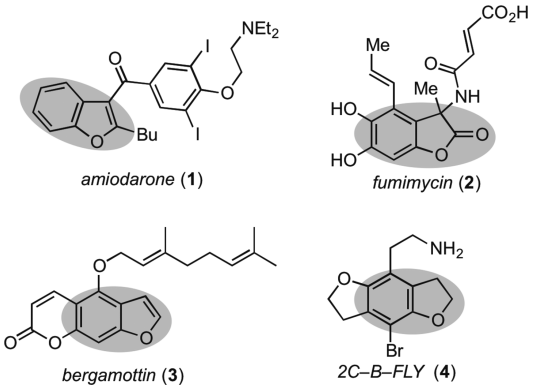
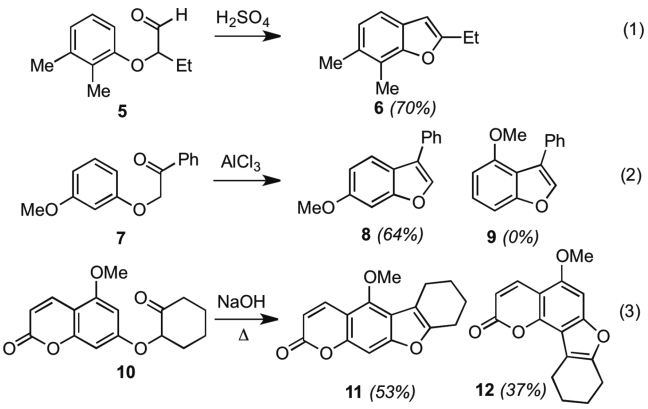


Figure 1. Medicinal benzofurans and benzofuranones.

natural product that displays antibiotic activity by inhibiting the bacterial protein deformylase enzyme.[3] Bergamottin (**3**) is a cytochrome P450 inhibitor found in citrus fruits, and it is implicated in grapefruit−drug interactions.[4] Finally, 2C-B-FLY (**4**) is a dihydrobenzofuran bioisostere of mescaline, which was prepared for SAR investigation of the serotonin receptors,[5] and it has been used as a recreational hallucinogen.[6]

The importance of biologically active benzofuran derivatives has fueled decades of research into their chemical synthesis.[7] A classical and common strategy for their synthesis is shown in Scheme 1. An α-phenoxycarbonyl compound undergoes cyclization (e.g., intramolecular Friedel−Crafts-type condensation) to build the five-membered furanoid ring.[8] 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

Scheme 1. Regiochemistry in α-Phenoxy Carbonyl Cyclizations



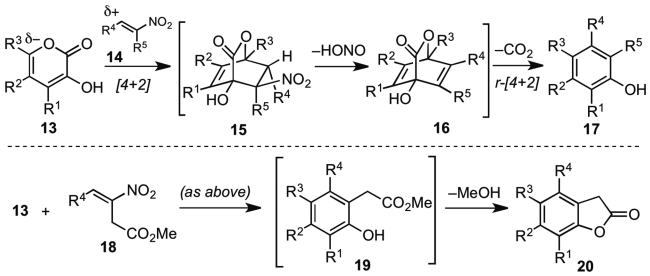
cyclization, and the product (**6**) is formed as a single regioisomer.[9] When both *ortho* positions are unsubstituted, the sterically less-hindered product is commonly favored. For example, cyclization of **7** leads to 3,6-disubstituted benzofuran **8**, and the 3,4-disubstituted congener **9** is not observed.[10] In cases where steric considerations do not provide a strong preference, regiochemical mixtures are common.[11] Cyclization of **10** leads to a mixture of **11** and **12** in a ratio of 53:37, respectively.[12]

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

Received: February 10, 2021
Published: April 14, 2021

https://doi.org/10.1021/acs.joc.1c00341
J. Org. Chem. 2021, 86, 6931−6936

Scheme 2. Diels–Alder Based Phenol and Benzofuranone Syntheses



of nitrous acid gives **16**.[14] Finally, retro-cycloaddition gives the product phenol (**17**). The key to this strategy is that both coupling partners are electronically polarized. The initial Diels–Alder reaction occurs with high levels of regioselectivity, and it tolerates substitution in both coupling partners. We are able to prepare many phenols with complete control of the substitution pattern.

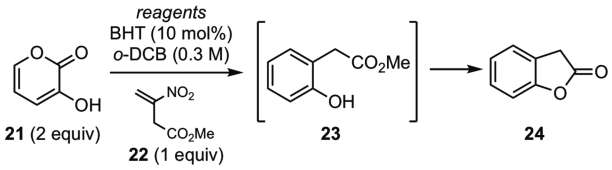
We speculated that if nitroalkenes bearing a carbomethoxymethyl group (**18**) were to participate in the reaction, phenols bearing a tethered ester (**19**) would be formed. Such nitroalkenes are conveniently prepared using standard Henry-type condensations of nitroalkanes.[15] We expected phenols **19** would cyclize to benzofuranones **20** under the reaction conditions.

Our investigations began with unsubstituted 3-hydroxy-2-pyrone (**21**) and nitroalkene **22** (Table 1). Conditions previously reported[13] for our substituted phenol synthesis (entry 1) promoted the desired reaction, giving phenol **23** in 53% yield and the desired benzofuranone product **24** in 15% yield. Allowing the reaction to proceed until there was complete consumption of starting materials **21**, **22**, and phenol intermediate **23** (TLC check) gave benzofuranone **24** in 45% yield (entry 2). Apart from the desired product (**24**), a multitude of minor products were present, but all were produced in less than ∼5% yield, and we were not able to determine their structure.

We were somewhat surprised to find that the formation of phenol **23** was faster than its conversion to benzofuranone **24** under the conditions in entries 1 and 2. In a control experiment, we found that isolation and subjection of phenol **23** to trifluoroacetic acid (TFA) rapidly gave **24** in 70% yield (see Supporting Information). Combining **21** and **22** with both the $AlCl_3$ Lewis acid and TFA protic acid markedly increased the rate of benzofuranone production (entry 3). Lowering the reaction temperature gave a slightly increased chemical yield of **24** (entry 4). Conducting the Diels–Alder-based cascade first with subsequent addition of TFA after consumption of **21** and **22** did not lead to improved yields (entry 5). Finally, conducting the reaction at 120 °C with 20 mol % of TFA gave an optimal yield of benzofuranone **24** (entry 6).

The benzofuranone synthesis was also evaluated using a variety of different Lewis acids. Boronic acids (entry 7), boron trifluoride (entry 8), and other aluminum Lewis acids (entry 9) all successfully promoted the reaction; however, the overall chemical yield was not improved. The protic acid used to affect ring closure was also varied. Toluenesulfonic acid (entry 10), hydrochloric acid (entry 11), and other weak acids such as trichloroacetic acid were evaluated (entry 12), but none of these acids gave superior results. Addition of molecular sieves

Table 1. Investigation of Conditions for the Benzofuranone Synthesis



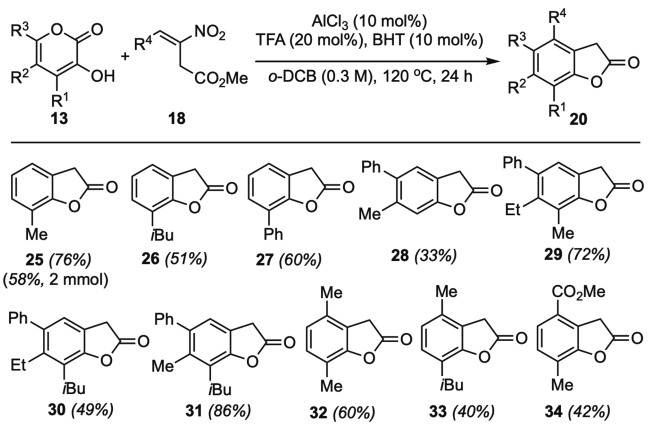
entry	reagents	T (°C)	time (h)	yield (%)[a]
1[b]	$AlCl_3$ (10 mol %)	150	2	53 (**23**) + 15 (**24**)
2	$AlCl_3$ (10 mol %)	150	24	45
3	$AlCl_3$ (10 mol %), TFA (10 mol %)	150	1	42
4	$AlCl_3$ (10 mol %), TFA (10 mol %)	110	24	58
5	i. $AlCl_3$ (10 mol %); ii. TFA (20 mol %)	120	20	53
6	**$AlCl_3$ (10 mol %), TFA (20 mol %)**	**120**	**20**	**64**
7	$PhB(OH)_2$ (10 mol %), TFA (20 mol %)	120	20	55
8	BF_3OEt_2 (10 mol %)	120	6	52
9	Me_2AlCl (10 mol %), TFA (20 mol %)	100	2.5	29 (**23**) + 30 (**24**)
10	$AlCl_3$ (10 mol %), pTsOH (20 mol %)	120	6	33
11	$AlCl_3$ (10 mol %), HCl (1 equiv)	150	1.5	32
12	$AlCl_3$ (10 mol %), Cl_3CCO_2H (20 mol %)	150	3	35
13	$AlCl_3$ (10 mol %), TFA (20 mol %), 4 Å MS	120	27	19
14[c]	$AlCl_3$ (10 mol %), TFA (20 mol %)	120	20	64

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

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**, $R^1 \neq H$) were efficiently converted to substituted benzofuranones **20**. Methyl (**25**), branched alkyl (**26**), and phenyl groups (**27**) were all well tolerated. Pyrones

Scheme 3. Regioselective Syntheses of Benzofuranones

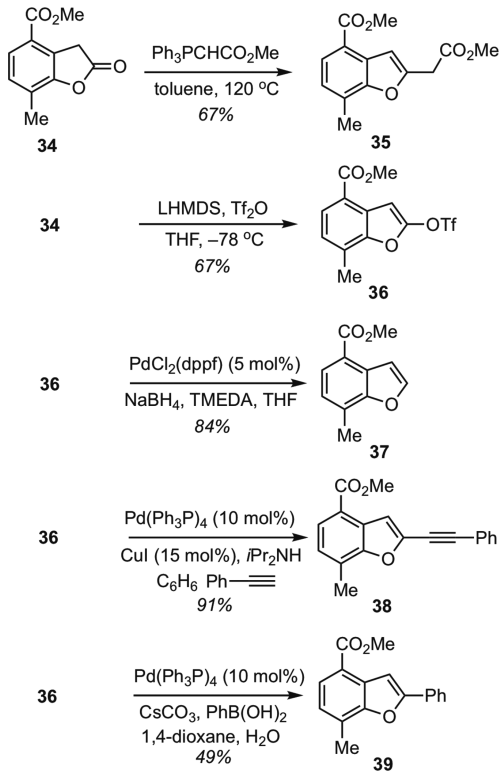


https://doi.org/10.1021/acs.joc.1c00341
J. Org. Chem. 2021, 86, 6931–6936

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 olefinated 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]

Scheme 4. Synthesis of Substiuted Benzofurans



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 CaH_2 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 (^{1}H NMR and ^{13}C NMR) were recorded in deuterated chloroform ($CDCl_3$) 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 $AlCl_3$ (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-2*H*-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 (17.1 mg, 64%). Spectroscopic data for **24** matched those previously reported.[21]

*7-Methylbenzofuran-2(3H)-one (**25**).* 3-Hydroxy-4-methyl-2*H*-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 4 h. Purification by FCC (20:1 hexanes/EtOAc) yielded **25** as a solid (22.4 mg, 76%). Spectroscopic data for **25** matched those previously reported.[21]

*Large scale synthesis of 7-methylbenzofuran-2(3H)-one (**25**).* 3-Hydroxy-4-methyl-2*H*-pyran-2-one (378 mg, 3.0 mmol) and methyl 3-nitrobut-3-enoate (290 mg, 2.0 mmol) were subjected to the general procedure for 10 h. Purification by FCC (20:1 hexanes/EtOAc) yielded **25** as a solid (173 mg, 58%).

*7-Isobutylbenzofuran-2(3H)-one (**26**).* 3-Hydroxy-4-isobutyl-2*H*-pyran-2-one (50.4 mg, 0.3 mmol) and methyl 3-nitrobut-3-enoate (21.75 mg, 0.15 mmol) were subjected to the general procedure for 6 h. Purification by FCC (20:1 hexanes/EtOAc) yielded **26** as an oil (14.4 mg, 51%). Data for **26**: R_f 0.51 (3:1 hexanes/EtOAc); IR (thin film) 2957, 1811, 1449 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.11 (d, J = 7.7 Hz, 1 H), 7.09 (d, J = 7.7 Hz, 1 H), 7.05 (t, J = 7.7 Hz, 1 H), 3.74 (s, 2 H), 2.54 (d, J = 7.0 Hz, 2 H), 1.96 (m, 1 H), 0.92 (d, J = 6.3 Hz, 6 H); ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$) δ 174.5, 153.3, 130.3, 125.0, 123.7, 122.7, 122.0, 38.8, 33.5, 29.0, 22.3; HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{12}H_{15}O_2$ 191.1072; Found 191.1079.

*7-Phenylbenzofuran-2(3H)-one (**27**).* 3-Hydroxy-4-phenyl-2*H*-pyran-2-one (28 mg, 0.15 mmol, 1.5 equiv) and methyl 3-nitrobut-3-enoate (14.5 mg, 0.1 mmol, 1 equiv) were subjected to the general procedure at 100 °C for 4 h. Purification by FCC (50:1 hexanes/EtOAc) yielded **27** as a solid (12.7 mg, 60%). Data for **27**: R_f 0.5 (3:1 hexanes/EtOAc); mp: 124–126 °C; IR (thin film) 1807, 1425 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.66 (m, 2 H), 7.48–7.44 (m, 3 H), 7.40–7.36 (m, 1 H), 7.27–7.20 (m, 2 H), 3.81 (s, 2 H); ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$) δ 174.0, 151.7, 135.3, 129.0, 128.7, 128.6,

https://doi.org/10.1021/acs.joc.1c00341
J. Org. Chem. 2021, 86, 6931–6936

128.0, 125.1, 124.5, 123.7, 123.5, 33.1; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{14}H_{11}O_2$ 211.0759; Found 211.0763.

*6-Methyl-5-phenylbenzofuran-2(3H)-one (**28**).* 3-Hydroxy-5-methyl-6-phenyl-2*H*-pyran-2-one (20.2 mg, 0.1 mmol, 1 equiv) and methyl 3-nitrobut-3-enoate (29 mg, 0.2 mmol, 2 equiv) were subjected to the general procedure. Purification by FCC (40:1 hexanes/EtOAc) yielded **28** as a solid (7.5 mg, 33%). Data for **28**: R_f 0.54 (3:1 hexanes/EtOAc); mp: 104−109 °C; IR (thin film) 3029, 2958, 2924, 1806, 1632, 1481, 1061 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.42 (t, J = 7.7 Hz, 2 H), 7.36 (t, J = 7.7 Hz, 1 H), 7.27 (d, J = 7.7 Hz, 2 H), 7.13 (s, 1 H), 7.02 (s, 1 H), 3.74 (s, 2 H), 2.27 (s, 3 H); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$) δ 174.6, 154.0, 141.1, 138.1, 136.8, 129.3, 128.3, 127.1, 125.8, 120.3, 112.2, 32.9, 21.0; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{13}O_2$ 225.0916; Found 225.0897.

*6-Ethyl-7-methyl-5-phenylbenzofuran-2(3H)-one (**29**).* 5-Ethyl-3-hydroxy-4-methyl-6-phenyl-2*H*-pyran-2-one (34.5 mg, 0.15 mmol, 1 equiv) and methyl 3-nitrobut-3-enoate (55 mg, 0.375 mmol, 2.5 equiv) were subjected to the general procedure at 100 °C. Purification by FCC (20:1 hexanes/EtOAc) yielded **29** as a solid (27.3 mg, 72%). Data for **29**: R_f 0.60 (4:1 hexanes/EtOAc); mp: 82−85 °C; IR (thin film) 2968, 1807, 1627, 1447, 1082 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44−7.34 (m, 3 H), 7.26−7.24 (m, 2 H), 6.95 (s, 1 H), 3.75 (s, 2 H), 2.57 (q, J = 7.2 Hz, 2 H), 2.35 (s, 3 H), 0.99 (t, J = 7.2 Hz, 3 H); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$) δ 174.7, 153.2, 142.0, 141.7, 138.2, 129.3, 128.1, 126.3, 123.4, 119.4, 119.3, 33.6, 23.3, 14.7, 11.9; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{17}O_2$ 253.1229; Found 253.1221.

*6-Ethyl-7-isobutyl-5-phenylbenzofuran-2(3H)-one (**30**).* 5-Ethyl-3-hydroxy-4-isobutyl-6-phenyl-2*H*-pyran-2-one (27 mg, 0.1 mmol, 1 equiv) and methyl 3-nitrobut-3-enoate (29 mg, 0.2 mmol, 2 equiv) were subjected to the general procedure for 3 h. Purification by FCC (100% hexanes then 20:1 hexanes/EtOAc) yielded **30** as an oil (14.3 mg, 49%). Data for **30**: R_f 0.63 (5:1 hexanes/EtOAc); IR (thin film) 2958, 1809, 1445, 1102 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.40 (t, J = 7.0 Hz, 2 H), 7.35 (t, J = 7.0 Hz, 1 H), 7.26 (d, J = 7.0 Hz, 2 H), 6.94 (s, 1 H), 3.74 (s, 2 H), 2.63 (d, J = 7.7 Hz, 2 H), 2.60 (q, J = 7.0 Hz, 2 H), 2.00 (m, 1 H), 0.98 (d, J = 7.0 Hz, 6 H), 0.90 (t, J = 7.7 Hz, 3 H); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$) δ 174.8, 153.4, 142.2, 141.8, 138.5, 129.4, 128.0, 126.9, 123.8, 123.4, 119.4, 35.3, 33.5, 29.4, 22.7, 22.6, 15.4; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{23}O_2$ 295.1698; Found 295.1685.

*7-Isobutyl-6-methyl-5-phenylbenzofuran-2(3H)-one (**31**).* 3-Hydroxy-4-isobutyl-5-methyl-6-phenyl-2*H*-pyran-2-one (26 mg, 0.10 mmol, 1 equiv) and methyl 3-nitrobut-3-enoate (36 mg, 0.25 mmol, 2.5 equiv) were subjected to the general procedure at 100 °C for 6 h. Purification by FCC (50:1 hexanes/EtOAc) yielded **31** as a solid (24.1 mg, 86%). Data for **31**: R_f 0.51 (5:1 hexanes/EtOAc); mp: 130−132 °C; IR (thin film) 2957, 2868, 1809, 1452, 1102 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43−7.39 (m, 2 H), 7.35 (tt, J = 6.4, 1.6 Hz, 1 H), 7.26−7.24 (m, 2 H), 6.99 (s, 1 H), 3.75 (s, 2 H), 2.64 (d, J = 7.2 Hz, 2 H), 2.18 (s, 3 H), 1.98 (m, 1 H), 0.98 (d, J = 6.8 Hz, 6 H); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$) δ 174.8, 153.2, 142.2, 138.7, 135.2, 129.4, 128.2, 126.9, 124.1, 123.3, 119.5, 35.9, 33.6, 28.8, 22.6, 17.2; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{21}O_2$ 281.1542; Found 281.1531.

*4,7-Dimethylbenzofuran-2(3H)-one (**32**).* 3-Hydroxy-4-methyl-2*H*-pyran-2-one (50.4 mg, 0.4 mmol) and methyl-3-nitropent-3-enoate (31.8 mg, 0.2 mmol) were subjected to the general procedure at 150 °C for 3 days. Purification by FCC (20:1 hexanes/EtOAc) yielded **32** as a solid (19.4 mg, 60%). Spectroscopic data for **32** matched those previously reported.[22]

*7-Isobutyl-4-methylbenzofuran-2(3H)-one (**33**).* 3-Hydroxy-4-isobutyl-2*H*-pyran-2-one (50 mg, 0.30 mmol) and methyl-3-nitropent-3-enoate (24 mg, 0.15 mmol) were subjected to the general procedure at 150 °C for 22 h. Purification by FCC (20:1 hexanes/EtOAc) yielded **33** as an oil (12.3 mg, 40%). Data for **33**: R_f 0.6 (4:1 hexanes/EtOAc); IR (thin film) 2956, 1807, 1419, 1124 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 6.99 (d, J = 7.7 Hz, 1 H), 6.87 (d, J = 7.7 Hz, 1 H), 3.64 (s, 2 H), 2.50 (d, J = 7.7, 2 H), 2.25 (s, 3 H), 1.93 (m, 1 H), 0.91 (d, J = 7.0 Hz, 6 H); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$) δ 174.6, 152.9, 131.9, 130.1, 124.7, 122.0, 121.7, 38.6, 32.6, 29.0, 22.3, 18.5; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{13}H_{17}O_2$205.1229; Found 205.1226.

*Methyl 7-Methyl-2-oxo-2,3-dihydrobenzofuran-4-carboxylate (**34**).* 3-Hydroxy-4-methyl-2*H*-pyran-2-one (38 mg, 0.30 mmol) and dimethyl-3-nitropent-2-enedioate (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 (13.1 mg, 42%). Data for **34**: R_f 0.43 (5:1 hexanes/EtOAc); mp: 123−124 °C. IR (thin film) 2956, 1804, 1706, 1304 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) 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); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$) 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 $C_{11}H_{11}O_4$ 207.0657; Found 207.0667.

*Methyl 2-(2-Methoxy-2-oxoethyl)-7-methylbenzofuran-4-carboxylate (**35**).* To a thick-walled reaction vessel was added methyl 7-methyl-2-oxo-2,3-dihydrobenzofuran-4-carboxylate (20.6 mg, 0.1 mmol, 1 equiv), methyl (triphenyl 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 120 °C for 14 h. The reaction mixture was cooled to rt, and the mixture was directly purified by FCC (16:1:1 hexanes/EtOAc/CH_2Cl_2) without aqueous workup to yield **35** as a solid (17.6 mg, 67%). Data for **35**: R_f 0.375 (5:1 hexanes/EtOAc); mp: 77−80 °C; IR: (thin film) 2953, 1745, 1714, 1599, 1435, 1266, 1198 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) 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); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$) δ 169.2, 167.1, 154.2, 152.2, 128.5, 126.8, 125.7, 124.6, 120.0, 106.8, 52.6, 51.9, 34.6, 15.5; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{14}O_5Na$ 285.0739; Found 285.0750.

*Methyl 7-Methyl-2-(((trifluoromethyl)sulfonyl)oxy)benzofuran-4-carboxylate (**36**).* To 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, 1.05 mmol, 2 equiv) at −78 °C. The mixture was stirred at −78 °C for 1 h, upon which time trifluoromethanesulfonic anhydride (266 mg, 0.94 mmol, 1.8 equiv) was added dropwise. The mixture was stirred at −78 °C for an additional 1 h. The mixture was quenched with water (20 mL) and extracted with EtOAc (4 × 30 mL). The combined organic layers were dried over Na_2SO_4, 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**: R_f 0.57 (5:1 hexanes/EtOAc); mp: 39−40 °C; IR: (thin film) 2956, 1722, 1600, 1439, 1230 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) 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); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$) 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 $C_{12}H_{10}O_6F_3S$ 339.0150; Found 339.0154.

*Methyl 7-Methylbenzofuran-4-carboxylate (**37**).* A solution of methyl 7-methyl-2-(((trifluoromethyl)sulfonyl)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. $PdCl_2$(dppf) (2.8 mg, 0.00375 mmol, 5 mol %), TMEDA (30 mg, 0.255 mmol, 3.4 equiv), and $NaBH_4$ (9.7 mg, 0.255 mmol, 3.4 equiv) were sequentially added. The mixture was stirred at rt for 1.5 h. The reaction was quenched with brine (15 mL) and extracted with EtOAc (4 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by FCC (40:1 hexanes:EtOAc) to yield **37** as an oil (11.9 mg, 84%). Data for **37**: R_f 0.55 (10:1 hexanes/EtOAc); IR: (thin film) 2951, 1715, 1280 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.89 (d, J = 7.7 Hz, 1 H), 7.74 (s, 1 H), 7.36 (s, 1 H), 7.15 (d, J = 7.7 Hz, 1 H), 3.97 (s, 3 H), 2.59 (s, 3 H); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$) δ 167.1, 154.2, 146.3, 127.4, 127.2, 125.7, 124.7, 120.4, 108.0, 51.9, 15.5; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{11}H_{11}O_3$ 191.0708; Found 191.0714.

https://doi.org/10.1021/acs.joc.1c00341
J. Org. Chem. 2021, 86, 6931−6936

*Methyl 7-Methyl-2-(phenylethynyl)benzofuran-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. Phenylacetylene (15.3 mg, 0.15 mmol, 2 equiv), CuI (2.1 mg, 0.01125 mmol, 15 mol %), diisoproylamine (30 mg, 0.3 mmol, 4 equiv), and $Pd(PPh_3)_4$ (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 NH_4Cl solution (15 mL) and extracted with EtOAc (4 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by FCC (40:1 hexanes/EtOAc) to yield **38** as a solid (19.7 mg, 91%). Data for **38**: R_f 0.32 (20:1 hexanes/EtOAc); mp: 71−76 °C; IR: (thin film) 2950, 1716, 1270 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) 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); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$) 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 $C_{19}H_{15}O_3$ 291.1021; Found 291.1022.

*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 M) was added phenylboronic acid (9.2 mg, 0.075 mmol, 1.5 equiv). The mixture was cooled to 0 °C, and then $Pd(PPh_3)_4$ (5.8 mg, 0.005 mmol, 10 mol %) and $CsCO_3$ (49 mg, 0.15 mmol, 3 equiv) were added at once. 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 Na_2SO_3, filtered, and concentrated. The residue was purified by FCC (50:1 hexanes/EtOAc) to yield **39** as a solid (6.5 mg, 49%). Data for **39**: R_f 0.25 (20:1 hexanes/EtOAc); mp: 58−61 °C; IR: (thin film) 2953, 1714, 1434, 1269, 1200 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) 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 (t, J = 7.7 Hz, 2 H), 7.39 (t, 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); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$) 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 $C_{17}H_{15}O_3$ 267.1021; Found 267.1028.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00341.

Detailed procedures for the synthesis of nitroalkenes, depiction of ^1H and ^{13}C NMR spectra of all products (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors acknowledge financial support from the National Science Foundation (CHE-1956401) and Oregon State University.

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J. Org. Chem. 2021, 86, 6931−6936