Dihydrobenzofuran Synthesis by an Anodic [3 + 2] Cycloaddition of Phenols and Unactivated Alkenes

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Several biologically active dihydrobenzofurans have recently been found,[1] and new synthetic methods have also been extensively investigated.[2] Inter- and intramolecular cyclization reactions play important roles in the construction of dihydrobenzofurans. The intermolecular reaction of carbon nucleophiles with electrochemically generated intermediates can provide a unique means for generating new carbon−carbon bonds, and this method may also be used to generate reactive intermediates to construct dihydrobenzofuran skeletons under mild conditions (Scheme 1). Direct electrooxidation of phenol derivatives[3] in the presence of electron-rich vinyl ethers gave unique dihydrobenzofuran skeletons. Vinyl sulfides have also been found to act as nucleophiles for the electrogenerated phenoxonium cation intermediate. From the corresponding cycloadducts, alkylsulfanyl groups can be removed by acid treatment. Therefore, the cycloaddition reaction of vinyl sulfides is important in the construction of benzofurans without activating functional groups. On the other hand, it is difficult to construct the corresponding dihydrobenzofurans directly by the [3 + 2] cycloaddition of unactivated alkenes with phenoxonium cation. In fact, the direct intermolecular attack of aliphatic alkenes has not yet been accomplished, even when they were added to the reaction mixture in excessive amounts.[4]

Generally, active carbon nucleophiles are unstable under electrooxidative conditions because most nucleophiles possess electron-rich heteroatoms or aromatic rings. Therefore, the electrolytic potentials are limited to the lower of those of the coexisting nucleophiles and those of the products.[5] Our interest in the cycloaddition of electrogenerated phenoxonium cation with unactivated alkenes for constructing varied dihydrobenzofuran skeletons led us to consider a new reaction system in which aliphatic alkenes themselves show high reactivity as nucleophiles and the overoxidation of products can also be avoided. We report here our successful direct synthesis of the desired dihydrobenzofurans.

Scheme 1

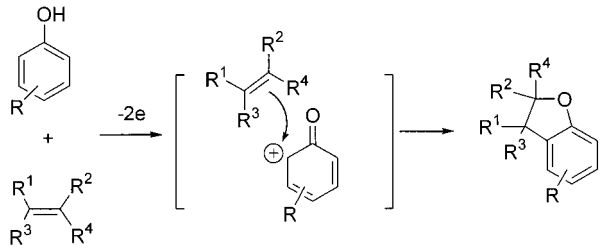

Table 1. Media Effect on the Anodic Dihydrobenzofuran Synthesis[a]

solvent	electrolyte	additives	yield (%)
CH_3CN	1.0 M $LiClO_4$	none	ND
CH_3CN	0.1 M Et_4NOTs	none	ND
CH_3CN	0.1 M Et_4NOTs	none	ND
THF	1.0 M $LiClO_4$	none	ND
CH_3NO_2	0.1 M Et_4NOTs	none	ND
CH_3NO_2	1.0 M $LiClO_4$	none	29
CH_3NO_2	3.0 M $LiClO_4$	none	55
CH_3NO_2	3.0 M $LiClO_4$	50 mM AcOH	98
CH_3NO_2	3.0 M $LiClO_4$	50 mM MsOH	ND

[a] Electrochemical oxidation of methyl 2,5-dihydroxybenzoate was performed at 1.0 V vs SCE using glassy carbon anode and Pt cathode in an undivided cell. [b] ND = not detected.

Scheme 2

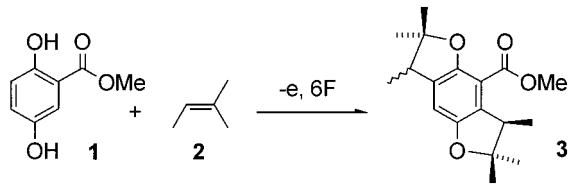

Table 1 summarizes the results for the optimization study using methyl 2,5-dihydroxybenzoate **1** and 2-methyl-2-butene **2** (Scheme 2). The reactions were all carried out by initially mixing the starting materials with the relevant electrolytes in solvents using a bare glassy carbon anode and a platinum plate cathode. Excessive charge (ca. 6 F/mol) was passed through the cell until the starting hydroquinone was no longer observed. Only in the combination of lithium perchlorate and nitromethane[6] was a dihydrobenzofuran **3** obtained in moderate yields. The yields increased in highly concentrated lithium perchlorate in nitromethane, and product **3** was finally obtained in excellent yield in the presence of acetic acid. On the other hand, the alkenes decomposed

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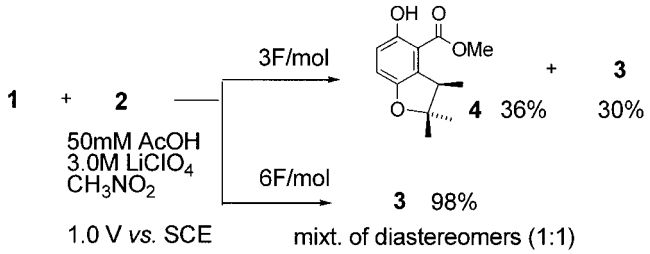
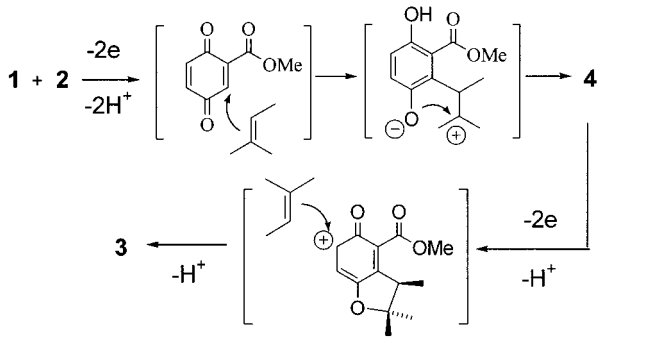
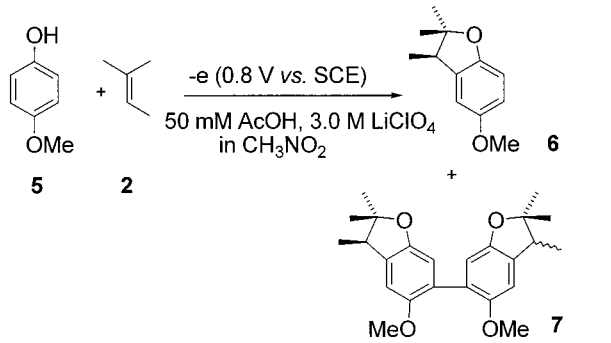
Scheme 3





Scheme 4



by the addition of methanesulfonic acid to give messy products. It is presumed that the moderate acidic condition by the addition of acetic acid assisted nucleophilic attack of the alkenes by stabilizing carbocation intermediates of corresponding alkenes. After 3 F/mol of charge had been passed through the cell, compounds **3** and **4** were isolated with the starting materials (Scheme 3). These results suggested that the oxidative addition reaction proceeded in a stepwise manner. First, the corresponding *p*-benzoquinone was generated to form compound **4** by Michael addition of **2**. The dihydrobenzofuran **4** was further oxidized to give a phenoxonium ion, which was attacked by another **2** to form a three-ringed product **3**. Anodic oxidation of 4-methoxyphenol **5** with **2** in the same reaction media gave a mixture of the desired dihydrobenzofuran **6** and dimerized product **7** (Scheme 4). Since dimerization occurred by the over-oxidation of **6**, we introduced a PTFE-fiber-coated electrode which was prepared by wrapping the electrode in PTFE strings.[7] This electrode was expected to selectively oxidize only polar starting materials, and compound **6** was successfully obtained in excellent yields. In this electrolytic cell, a less-polar cycloadduct **6** could be maintained predominantly on the surface of the PTFE resin, on which further electron transfer was avoided (Scheme 5). Using the electrolytic reaction system with

Scheme 5

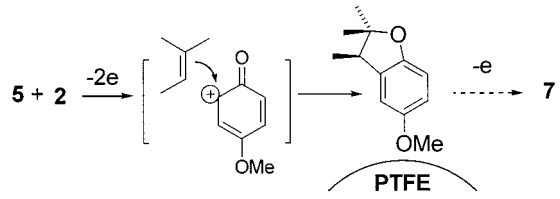
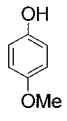
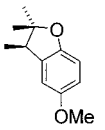
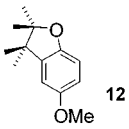
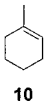
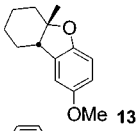
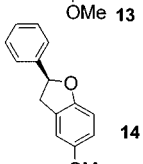
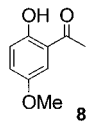
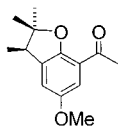
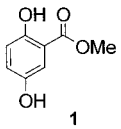
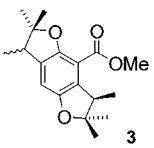


Table 2. Dihydrobenzofuran Derivatives via Anodic Intermolecular Cycloaddition of Phenols and Unactivated Alkenes[a]

substrate	$E_{ox.}$(*vs.* SCE)	alkene	products	yield (%)
 5	0.76			97
		 9	 12	95
		 10	 13	60
		 11	 14	96
 8	0.93		 15	99
 1	0.97		 3	98 (1:1)

[a] Electrochemical oxidation was performed in 3.0 M lithium perchlorate/nitromethane in the presence of acetic acid (50 mM) using a PTFE-fiber-coated glassy carbon anode.

the PTFE-fiber-coated glassy carbon anode, various unactivated alkenes were used for dihydrobenzofuran synthesis with phenols (Table 2). Styrene also gave the corresponding cycloadduct **14**, which had been difficult to obtain by usual methods. The electrooxidation of 1-(2-hydroxy-5-methoxyphenyl)ethan-1-one **8**, which showed a higher oxidation potential and lower electron density as an electrophile, also gave the corresponding cycloadduct **15** in excellent yields.

The present [3 + 2] cycloaddition reaction was completed in a solution of lithium perchlorate in nitromethane in the presence of acetic acid. Highly concentrated lithium perchlorate ions in nitromethane might promote

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the electron transfer of phenols by stabilizing the electrogenerated intermediates. In addition, we can presume that the ionic polar solvent system also stabilizes the carbocation intermediates to increase the nucleophilicity of unactivated alkenes.

Experimental Section

NMR spectra were measured on JEOL EX-270 and EX-400 spectrometers at 270, 400 (^{1}H) and 67.9, 100.6 (^{13}C) MHz for samples in $CDCl_3$, containing tetramethylsilane as internal standard. Redox potentials were measured by cyclic voltammetry (Yanaco, P-900 cyclic polarograph) by using a glassy carbon as anode and a Pt wire as cathode vs SCE. The anode for the macroelectrolysis was prepared by wrapping a glassy carbon plate (60 × 20 × 2 mm) in the PTFE strings (composed of the PTFE-fibers 20 μm × 1 m, 2.0 g, Flon Industry) to completely cover the surface of the anode. The electrodes were equipped in a test tube (diameter 25 mm) and capped with a silicon rubber. By using a SCE as reference electrode, the electrolysis was performed at a constant potential under Ar atmosphere at ambient temperature.

General Procedure of the Electrochemical Reactions. Phenol (1.0 mmol), alkene (2.0 mmol), and AcOH (1.0 mmol) were added to 3.0 M $LiClO_4$−CH_3NO_2 (20 mL). The reaction cell was capped with a septum equipped with the PTFE-fiber-coated glassy carbon anode, the Pt cathode (10 mm × 10 mm), and the SCE. Under Ar atmosphere the electrolysis was then performed at the peak oxidation potentials of the substrates given in Table 2. After the reaction was completed (ca. 2.8 F/mol), the reaction mixture was poured into AcOEt, and the AcOEt solution was successively washed with 5% aq $NaHCO_3$ and brine. The organic layer was dried over anhydrous $MgSO_4$. After filtration and evaporation under reduced pressure, the residue was purified by silica gel column chromatography using hexane−AcOEt to give cycloadducts.

Methyl 2,2,3,6,6,7-Hexamethyl-2,3,6,7-tetrahydrofurano-[2′,3′-3,2]benzo[5,6-*b*]furan-4-carboxylate (3). A 1:1 mixture of diastereomers. Yellow oil (98%). Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 70.98; H, 7.88. MS, *m*/*z* (%), 304 (M^+, 100), 257 (86), 229 (51). IR (NaCl) 2971, 1731, 1434, 1114 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.67 (s, 1H), 6.66 (s, 1H), 3.88 (s, 6H), 3.42 and 3.39 (q, J = 7.0 Hz, 1H, 2 × C*H*Me), 3.11 and 3.03 (q, J = 7.0 Hz, 1H, 2 x C*H*Me), 1.52, 1.46, 1.42, 1.41, 1.33, 1.25, 1.19 and 1.17 (s, 12H, 8 x CH_3), 1.32 (d, J = 7.0 Hz, 3H, 2 x CH_3), 1.10 and 1.08 (d, J = 7.0 Hz, 3H, 2 x CH_3). ^{13}C NMR ($CDCl_3$) δ 166.0, 152.9, 151.8, 134.2, 133.2, 133.0, 110.5, 110.2, 90.7, 90.2, 88.4, 51.7, 46.5, 45.6, 28.4, 28.2, 27.9, 22.6, 22.2, 21.9, 16.7, 15.1, 14.3. UV λ_{max} [EtOH] (log ϵ) 352 (3.67), 222 (4.10).

5-Methoxy-2,2,3-trimethyl-2,3-dihydrobenzo[*b*]furan (6). Yellow oil (97%). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C,74.80; H,8.31; HRMS Calcd for 192.1150. Found: 192.1143. MS, *m*/*z* (%), 192 (M^+, 90), 177 (100). IR (NaCl) 2967, 1486, 1251 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.68 (dd, J = 2.14, 1.00 Hz, 1H), 6.63 (m, 1H), 6.62 (m, 1H), 3.75 (s, 3H), 3.12 (q, J = 7.0 Hz, 1H), 1.45 (s, 3H), 1.26 (s, 3H), 1.21 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 153.82, 152.00, 133.92, 112.37, 110.63, 109.25, 89.51, 56.03, 46.18, 27.99, 21.96, 14.66. UV λ_{max} [EtOH] (log ϵ) 298 (3.37), 222 (4.10).

5-Methoxy-6-(5-methoxy-2,2,3-trimethyl-2,3-dihydrobenzo[3,4-*b*]furan-6-yl)-2,2,3-trimethyl-2,3-dihydrobenzo[*b*]furan (7). Yellow oil (33%). Anal. Calcd for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91. Found: C, 75.21; H, 8.10. IR (NaCl) 2971, 1483, 1253 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.73 (s, 2H), 6.60 (s, 2H), 3.71 (s, 6H), 3.19 (q, J = 7.09 Hz, 2H), 1.28 (s, 6H), 1.29 (s, 6H), 1.26 (d, J = 7.09 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 151.51, 151.10, 131.99, 127.30, 112.09, 112.07, 108.28, 89.42, 60.41, 56.87, 46.39, 28.24, 28.22, 22.17, 21.14, 14.68, 14.62, 1430; UV λ_{max} [EtOH] (log ϵ) 301 (4.34).

5-Methoxy-2,2,3,3-tetramethyl-2,3-dihydrobenzo[*b*]furan (12). Yellow oil (95%). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.52; H, 9.01. HRMS Calcd for 206.1307. Found: 206.1320. MS, *m*/*z* (%), 206 (M^+, 100), 191 (99). IR (NaCl) 2975, 1488, 1211, 1112 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 6.66 (m, 1H), 6.63 (m, 1H), 6.63 (m, 1H), 3.76 (s, 3H), 1.31 (s,6H), 1.18 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 153.89, 151.02, 139.02, 111.70, 109.45, 109.33, 91.54, 55.91, 46.48, 23.95, 22.87. UV λ_{max} [EtOH] (log ϵ) 295 (4.58), 224 (4.78).

8-Methoxy-4a-methyl-1,2,3,4,4a,9b-hexahydrobenzo[*b*]-benzo[2,1-*d*]furan (13). Yellow oil (60%). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.03; H, 8.51. MS, *m*/*z* (%), 218 (M^+, 100), 175 (38). IR (NaCl) 2933, 1483 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.69 (m, 1H), 6.65 (m, 2H), 3.78 (s, 3H), 3.09 (t, J = 5.13, 1H), 1.74 (m, 5H), 1.50 (s, 3H), 1.30 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 153.84, 152.52, 133.51, 111.87, 110.12, 109.80, 88.55, 55.97, 47.31, 33.93, 25.92, 25.38, 22.05, 21.18. UV λ_{max} [EtOH] (log ϵ) 297 (4.57), 279 (4.78).

5-Methoxy-2-phenyl-2,3-dihydrobenzo[*b*]furan (14). Yellow oil (96%). Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.54; H, 6.40. HRMS Calcd for 226.0994. Found: 226.0975. MS, *m*/*z* (%), 226 (M^+, 100), 225 (33), 165 (87). IR (NaCl) 3068, 2940, 1488 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.40 (m, 5H), 6.79 (m, 2H), 6.67 (m, 1H), 5.73 (dd, J = 9.40, 8.24 Hz, 1H), 3.76 (s, 3H), 3.60 (dd, J = 15.83, 9.40 Hz, 1H), 3.20 (dd, J = 15.83, 8.24 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 154.09, 153.57, 141.84, 128.51, 127.87, 127.38, 125.65. 112.86, 111.08, 109.10, 84.19, 56.03, 38.91. UV λ_{max} [EtOH] (log ϵ) 310 (3.34).

1-(5-Methoxy-2,2,3-trimethyl-2,3-dihydrobenzo[2,3-*b*]furan-7-yl)ethan-1-one (15). Yellow oil (99%). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.60; H, 7.92. HRMS Calcd for 234.1256, Found 234.1263; MS, *m*/*z* (%), 234 (M^+, 100), 219 (74), 177 (86), 173 (79). IR (NaCl) 2975, 1673, 1463 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.16 (d, J = 2.64 Hz, 1H), 6.87 (d, J = 2.64 Hz, 1H), 3.79 (s, 3H), 3.13 (q, J = 7.10 Hz, 1H), 2.61 (s, 3H), 1.51 (s, 3H), 1.30 (s, 3H), 1.23 (d, J = 7.10 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 196.86, 153.47, 153.44, 136.94, 119.83, 118.04, 108.49, 91.10, 55.98, 45.27, 31.35, 28.05, 22.18, 14.56. UV λ_{max} [EtOH] (log ϵ) 353 (4.08), 250 (3.84), 221 (4.13).

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Supporting Information Available: ^{1}H NMR spectra of **3**, **4**, **6**, **7**, **12**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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