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A new approach to benzofuran synthesis: Lewis acid mediated cycloaddition of benzoquinones with stilbene oxides

Ken Kokubo *, Kenji Harada, Eiko Mochizuki, Takumi Oshima *

Division of Applied Chemistry, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

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ABSTRACT

We report a BF_3-mediated novel dehydrative cycloaddition reaction of benzoquinones with stilbene oxides to afford 2,3-diaryl-5-hydroxybenzofurans and 2,3-diaryl-5-hydroxydihydrobenzofurans in good combined yields. No change in the products or the yield is observed when using diphenylacetaldehyde and *cis*-stilbene oxide instead of *trans*-stilbene oxides. When stilbene oxide is reacted with hydroquinone instead of the corresponding benzoquinone under the same conditions, dihydrobenzofuran is isolated in high yield. On the basis of these results, we propose the following possible reaction mechanism: stilbene oxide is converted to a phenonium ion (the key intermediate), which undergoes nucleophilic attack by benzoquinone or the simultaneously generated hydroquinone and subsequent dehydrative intramolecular cyclization to afford benzofuran or dihydrobenzofuran, respectively.

Benzofurans and dihydrobenzofurans are present in a wide variety of natural products[1] and have attracted considerable attention owing to their biological[2] and pharmacological activities.[3] Hence, several researchers have focused on the development of new methods for synthesizing these useful compounds.[4] In general, phenols[5] and their ether derivatives[6] have been frequently employed as starting materials for benzofuran synthesis, whereas quinones have been used sparingly because they are much less nucleophilic than phenols. Benzoquinones that are used for the synthesis of *dihydrobenzofurans* react with alkenes after being activated by a Lewis acid.[7] However, the conversion of dihydrobenzofurans to the corresponding *benzofurans* requires high-temperature heating of the precursor dihydrobenzofuran with an appropriate leaving group;[8] and hence, benzofurans have been synthesized only via the photochemical intramolecular cyclization of vinyl-substituted quinones.[9]

Oxirane, which can be easily synthesized from alkene, is a versatile synthon having a highly strained three-membered heterocyclic ring with labile C–O bonds and is well known to undergo acid-induced nucleophilic ring opening[10] or Meinwald rearrangement to afford a carbonyl compound.[11] However, the cycloaddition reaction of quinones with oxiranes instead of alkenes has not been explored so far.

In this Letter, we wish to report the successful and facile synthesis of benzofurans and dihydrobenzofurans via the Lewis acid mediated reaction of oxiranes with benzoquinones.

The reaction of 2,6-dimethylbenzoquinone **1a** with *trans*-stilbene oxide **2a** (2 equiv) in the presence of $BF_3{\cdot}Et_2O$ (3 equiv) was carried out in chloroform at room temperature for 1 h to give 5-hydroxybenzofuran **3aa** (77% yield based on **1a** used) along with a fair amount of 5-hydroxydihydrobenzofuran **4aa** (17%) (Table 1, entry 1). The structures of **3aa** and **4aa** (trans-isomer) were determined by ^1H and ^{13}C NMR analysis and further confirmed by a single-crystal X-ray structural analysis of the representative **3aa** and **3ba**.[12] The ^1H NMR spectrum of **4aa** showed two sets of doublet protons at 5.46 and 4.45 ppm, which were assigned to the C2 and C3 methine protons, respectively. From the value of the coupling constant (J = 5.9 Hz) for these doublets, it was confirmed that **4aa** was present as the trans-isomer.[13]

The reaction of **1a** with *cis*-stilbene oxide (*cis*-**2a**) also afforded **3aa** and **4aa** (with the same trans stereochemistry), and the product yields were almost identical to those obtained when using *trans*-**2a** (entry 2). Interestingly, when monitoring the reaction by ^1H NMR, we found that **2a** rapidly underwent Meinwald rearrangement[11] under the present reaction conditions to afford diphenylacetaldehyde **2′**. Hence, we reacted **1a** with **2′** instead of **2a** and found that **2′** was consumed slowly during the reaction; the products obtained were the same as those obtained when using **2a** (entry 3).

We then carried out the reaction of **1a** with **2a** under the same conditions but in the presence of different Lewis acids. With the use of $BF_3{\cdot}Et_2O$, we achieved a high conversion efficiency and high combined yield within 1 h; however, the use of other Lewis acids such as $AlCl_3$, $SnCl_4$, $TiCl_4$, and $B(C_6F_5)_3$ resulted in a decrease in the conversion efficiency (entries 4–7). Relatively weak Lewis

* Corresponding authors. Tel.: +81 6 6879 4592; fax: +81 6 6819 4593 (K.K.).
E-mail addresses: kokubo@chem.eng.osaka-u.ac.jp (K. Kokubo), oshima@chem.eng.osaka-u.ac.jp (T. Oshima).

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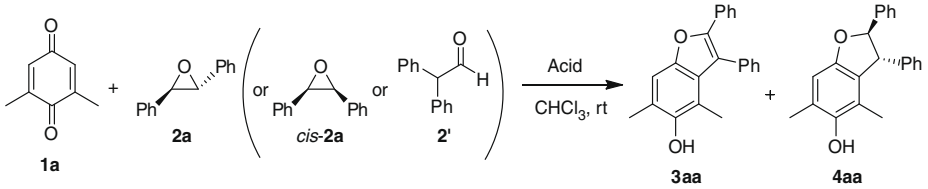
Table 1
Acid-mediated cycloaddition of benzoquinone **1a** with **2a**, *cis*-**2a**, and **2′**[a]



1a **2a** *cis*-**2a** **2′** **3aa** **4aa**

Entry	Compound	Acid	Time (h)	Conv (%)	Yield[b] (%)		
					3aa	**4aa**	Total
1	**2a**	$BF_3{\cdot}Et_2O$	1	100	77	17	94
2	*cis*-**2a**	$BF_3{\cdot}Et_2O$	1	100	75	20	95
3	**2′**	$BF_3{\cdot}Et_2O$	1	100	75	22	97
4	**2a**	$AlCl_3$	5	96	45	31	76
5	**2a**	$SnCl_4$	100	79	45	21	66
6	**2a**	$TiCl_4$	24	68	11	45	56
7	**2a**	$B(C_6F_5)_3$	40	7	7	0	7
8	**2a**	CH_3SO_3H	6	97	60	27	87
9	**2a**	CF_3SO_3H	0.1	100	63	33	96

[a] The reaction of **1a** (0.05 mmol) with **2a** (0.10 mmol) was carried out with 3 equiv of acid in chloroform at room temperature.
[b] Determined by ^1H NMR using fluorene as an internal standard based on **1a** used.

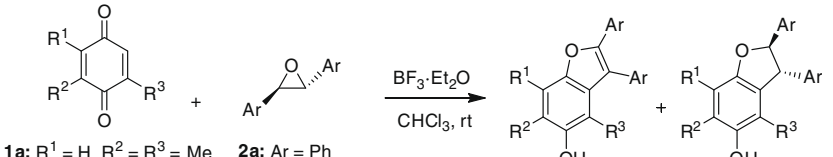
acids such as $TiCl_2(Et)_2$, $Ti(^iOPr)_4$, $Sc(OTf)_3$, and $MgBr_2$ were almost ineffective for the present reaction. Further, when we used $TiCl_4$, the product ratio of **3aa** to **4aa** was reversed, and **4aa** was isolated as the major product (45%) (entry 6). Protic acids such as CH_3SO_3H and CF_3SO_3H could also be successfully used in the present reaction; notably, the reaction time was reduced to a considerable extent when using CF_3SO_3H, a strong acid (entries 8 and 9).

As shown in Table 2, the extended reactions of various substituted benzoquinones **1a**–**f** with **2a** or the bis(4-tolyl)-substituted oxide **2b** could be carried out. The conversion efficiency in the reaction carried out using dimethoxy-substituted quinone **1b** was low, and the corresponding benzofuran **3ba** was isolated in moderate yield (47%) (entry 2). The reaction of dihalogenated quinones **1c** and **1d** with **2b** afforded benzofurans **3cb** and **3db** in low yields (36 and 57%), respectively, but no dihydrobenzofuran derivatives were detected in this case (entries 3 and 4). As expected, because of its apparent steric hindrance, the di(*t*-butyl)-substituted quinone **1e** remained unreacted even after 48 h (entry 5). However, the trisubstituted quinone **1f** could react with **2a** to give a highly substituted benzofuran **3fa** in good yield (76%) (entry 6).

In order to elucidate the reaction mechanism, we also conducted the reaction of 2,6-dimethylhydroquinone **5** with **2a** in the presence of $BF_3{\cdot}Et_2O$ under the same condition used for the reaction with **1**. Interestingly, **4aa** was obtained in high yield (80%), and no **3aa** was formed (Scheme 1). This result suggested that in the reaction of **1a** with **2a**, a small amount of **5** was formed, and it was converted to **4aa** immediately.

On the basis of these findings, we propose a plausible mechanism for our reaction (Scheme 2). Initially, phenonium ion **I** is generated as the key intermediate in the Meinwald rearrangement[11] of *trans*/*cis*-**2a** or from **2′** via a cationic intermediate **II**, by

Table 2
BF_3-mediated cycloaddition of benzoquinones **1a–f** with oxiranes **2a**,**b**[a]



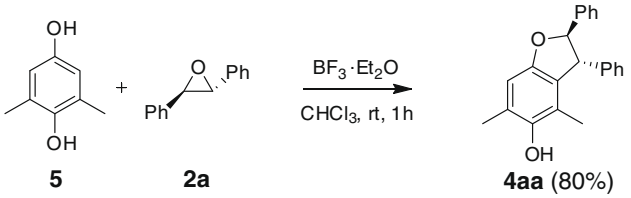
1a: R^1 = H, R^2 = R^3 = Me
1b: R^1 = H, R^2 = R^3 = MeO
1c: R^1 = H, R^2 = R^3 = Cl
1d: R^1 = H, R^2 = R^3 = Br
1e: R^1 = H, R^2 = R^3 = *t*-Bu
1f: R^1 = R^2 = MeO, R^3 = Me

2a: Ar = Ph
2b: Ar = 4-Tol

3 **4**

Entry	**1**	**2**	Time (h)	Conv (%)	Yield[b] (%)			
					3		**4**	
1	**1a**	**2a**	1	100	**3aa**	77	**4aa**	17
2	**1b**	**2a**	5	92	**3ba**	47	**4ba**	13
3	**1c**	**2b**	3	100	**3cb**	36		0
4	**1d**	**2b**	3	—[c]	**3db**	57[d]		0
5	**1e**	**2a**	48	2		0		0
6	**1f**	**2a**	10	83	**3fa**	76	**4fa**	7

[a] The reaction of **1** (0.05 mmol) with **2** (0.10 mmol) was carried out with 3 equiv of $BF_3{\cdot}Et_2O$ in chloroform at room temperature.
[b] Determined by ^1H NMR based on **1** used.
[c] Not determined.
[d] Isolated yield.

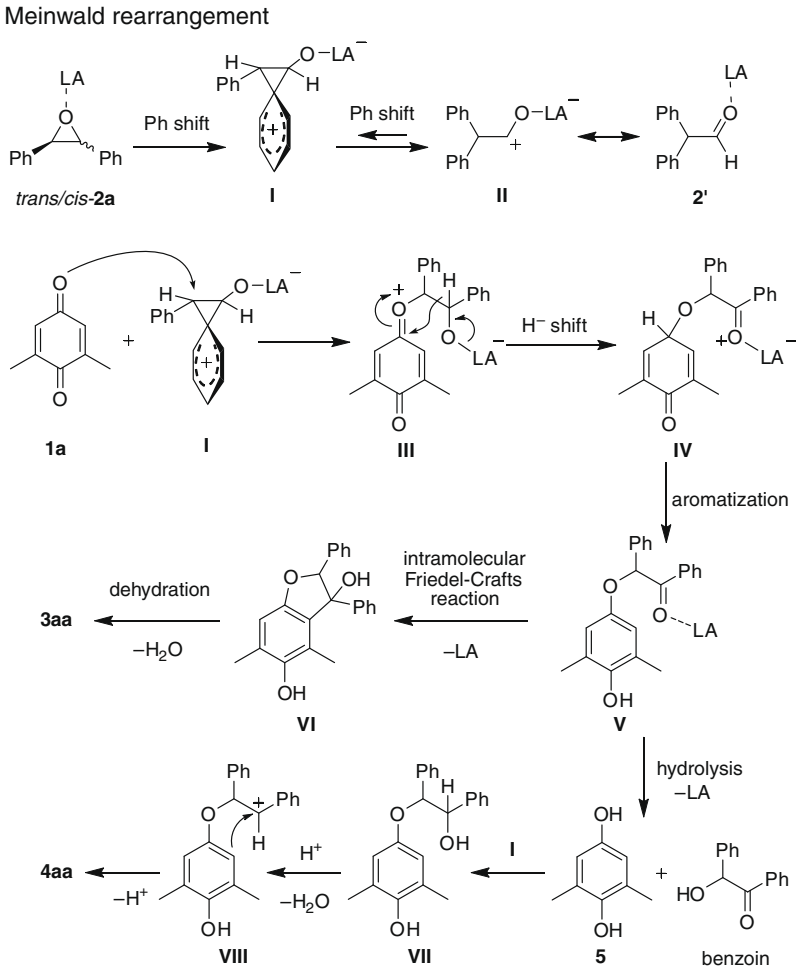


Scheme 1. BF_3-mediated cycloaddition of hydroquinone **5** with oxirane **2a.**

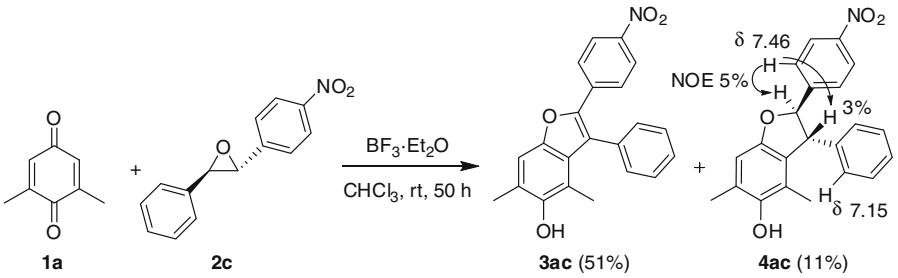
the complexation with Lewis acid in both cases. Then, quinone **1a** attacks the benzylic carbon of **I** from the less hindered side to form intermediate **III**. Intramolecular hydride shift of **III** leads to the formation of the **IV**, which then undergoes dienone–phenol rearrangement[14] to afford the intermediate **V**. Finally, intramolecular cyclization of **V** by Friedel–Crafts reaction and the successive dehydration of **VI** afford **3aa** as the major product. Under the present acidic conditions, **V** is hydrolyzed to form hydroquinone **5**, which attacks **I** in the manner described earlier to afford hydroquinol **VII**. Dehydrative intramolecular cyclization of **VII** then leads to the formation of **4aa**. The hydrolysis of **V** is confirmed by the fact that a small amount of benzoin (yield: 11%) is obtained as a byproduct in the reaction of **1a** with **2a**. Because of the bidentate nature of $TiCl_4$, Ti^{4+} ions form coordinate bonds with the carbonyl oxygen and phenol ether oxygen to form intermediate **V**, which is a five-membered metallacyclic complex; hydrolysis of **V** is then promoted, and **4aa** is formed preferentially.

The reaction of **1a** with an unsymmetrical oxirane **2c** which has an electron-withdrawing substituent was also carried out under the same conditions (Scheme 3). The corresponding benzofuran **3ac** and dihydrobenzofuran **4ac** were obtained in the yield of 51 and 11%, respectively. In both compounds, the nitrophenyl group was regioselectively introduced on the C2 position. The stereochemistry of **4ac** was determined as the trans-isomer from the value of the coupling constant (J = 6.0 Hz) and confirmed by the measurement of differential $^1H-^1H$ NOE as depicted in Scheme 3.[15] The reaction was strongly retarded by the effect of the electron-withdrawing nitro group and the conversion remained lower 69% even after 50 h.

In conclusion, we have designed a novel acid-induced dehydrative cycloaddition reaction of benzoquinones with stilbene oxides to give 2,3-diaryl-5-hydroxybenzofurans along with 2,3-diaryl-5-hydroxydihydrobenzofurans in moderate to high combined yields. The same products were obtained (with the same stereochemistry) when *cis*-stilbene oxide or diphenylacetaldehyde was used instead of *trans*-stilbene oxide, and the observed yields were essentially the same in both cases. When stilbene oxide was reacted with hydroquinone instead of the corresponding benzoquinone, dihydrobenzofuran was selectively formed in high yield. Thus, we concluded that the phenonium ion intermediate played a crucial role in the formation of benzofuran derivatives in the reaction involving nucleophilic attack by benzoquinone (for benzofuran formation) and hydroquinone (for dihydrobenzofuran formation). Further research is in progress for clarifying the details of the reaction mechanism and for investigating the scope and



Scheme 2. Proposed reaction mechanism for the BF_3-mediated cycloaddition of benzoquinone with oxirane.



Scheme 3. BF_3-mediated cycloaddition of benzoquinone **1a** with unsymmetrical oxirane **2c.**

limitations of the proposed reaction with a variety of substituents.

Acknowledgments

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Supplementary data

Supplementary data (compound data for new compounds **3aa**, **4aa**, **3ba**, **4ba**, **3cb**, **3db**, **3fa**, **4fa**, **3ac**, and **4ac** including ORTEP drawing and CIF files of **3aa** and **3ba**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.047.

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12. *General procedure for the preparation of **3aa** and **4aa***: To a solution of 2,6-dimethyl-1,4-benzoquinone (136 mg, 1 mmol) and *trans*-stilbene oxide (235 mg, 1.2 mmol) in dry chloroform (30 mL) was added boron trifluoride diethyl etherate (380 μL, 3 mmol) at room temperature. The mixture was stirred for 18 h, then quenched by the addition of water. The organic layer separated was dried over calcium chloride and concentrated in vacuo. The crude product was purified by silica gel column chromatography using hexane–ether as the eluent. 4,6-Dimethyl-2,3-diphenylbenzofuran-5-ol (**3aa**): colorless prisms; mp 125.5–126.0 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.89 (s, 3H), 2.37 (s, 3H), 4.44 (s, 1H), 7.19–7.23 (m, 4H), 7.38–7.49 (m, 7H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 11.29, 17.15, 109.69, 115.03, 118.32, 121.74, 126.14, 127.55, 127.67, 128.14, 128.65, 129.95, 130.69, 130.92, 134.62, 147.82, 148.33, 149.98; IR (KBr) 3454 (br, OH) cm^{-1}. Crystal structure of **3aa**: $C_{22}H_{18}O_2$, M = 314.4, monoclinic, space group $C12/c1$ with a = 22.656(2), b = 20.763(2), c = 18.899(2) Å, β = 129.202(1), V = 6889(1) Å^3, Z = 16, Dc = 1.220 g/cm^3, R = 0.0677, and Rw = 0.1780. 4,6-Dimethyl-2,3-diphenyl-2,3-dihydrobenzofuran-5-ol (**4aa**): colorless crystal; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.79 (s, 3H), 2.27 (s, 3H), 4.19 (s, 1H, OH), 4.45 (d, 1H, J = 5.9 Hz), 5.46 (d, 1H, J = 5.9 Hz), 6.65 (s, 1H), 7.13–7.44 (m, 10H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 12.46, 16.77, 58.03, 92.52, 108.33, 121.09, 123.69, 125.25, 126.39, 126.89, 127.70, 127.81, 128.53, 128.79, 141.97, 142.80, 146.38, 153.39; MS (EI) m/e = 316 (M^+); HRMS calcd for $C_{22}H_{20}O_2$: 316.1463. Found: 316.1472.
13. The coupling constants for trans-isomer of 4,6-substituted 2,3-diaryl-2,3-dihydrobenzofuran-5-ols were reported as J = 5.9 to 6 Hz (Ref. 7c).
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15. In Ref. 7b, the authors noted that coupling constants between the methine protons at C2 and C3 are not sufficient for assigning stereochemistry. However, the NOE data for dihydrobenzofurans **4** other than **4ac** could not be measured due to the overlap of the aromatic proton signals in ^{1}H NMR.