TBHP/TBAI-Promoted Oxidative Cyclization of *o*-Acylphenols for the Construction of 2-Aryloxybenzofuran-3(2*H*)-ones

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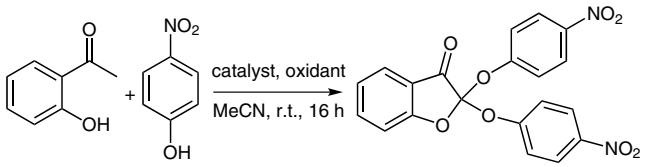
Abstract: An efficient metal-free approach to 2-aryloxybenzofuranonefuran-3(2*H*)-ones has been developed. Using *tert*-butyl hydroperoxide as oxidant and tetrabutylammonium iodide as catalyst, 2-acylphenols reacted with phenols to provide 2-aminobenzofuran-3(2*H*)-one derivatives in moderate to good yields.

Key words: *tert*-butyl hydroperoxide, TBHP, tetrabutylammonium iodide, TBAI, benzofuran-3(2*H*)-one, 2-acylphenol, oxidative cyclization

Benzofuran-3(2*H*)-ones (coumarones) play an important role in medicinal and pharmaceutical chemistry due to their broad pharmacological activities including in vitro antibacterial, anticancer, antifeedant, and antiparasitic activities.[1] They are also important intermediates for the synthesis of other bioactive compounds such as heliquinomycin analogues,[2a] a BK_{Ca} channel opener,[2b] and a 5-HT_{1A} receptor.[2c] Several traditional synthetic routes to the construction of benzofuran-3(2*H*)-one framework have been exploited, but most of these methods suffered from multisteps or harsh conditions.[3] Thus, development of convenient methods for the preparation of benzofuran-3(2*H*)-ones is still desirable. Oxidative cyclization of *o*-acylphenols was found to be a simple pathway for the synthesis of benzofuran-3(2*H*)-one derivatives.[4] However, excess $PhI(OAc)_2$ was used as oxidant for such a transformation and two equivalents of PhI were generated as a main byproduct, which caused this method less atom economical. Therefore, to find an alternative oxidant system for this oxidative cyclization process is quite necessary. In recent years, due to its high efficiency and environmental friendly properties, the *tert*-butyl hydroperoxide and tetrabutylammonium iodide (TBHP/TBAI) system has emerged as an attractive metal-free catalytic system and has been used successfully for the formation of carbon–carbon and carbon–heteroatom bonds.[5] In most cases, these reactions were carried out under mild conditions and only small molecules such as H_2O and *t*-BuOH were released as the main byproducts. With this novel method, varied synthetically or pharmaceutically useful compounds have been prepared in good yields. For example, Wan and his coworkers reported an efficient synthesis of imides,[5a] α-acyloxy ethers,[5e] allylic esters,[5f] *N*-nitrosamines,[5i] and α-amino acid esters[5j] using the TBHP/TBAI system. Herein, to extend the application of this protocol, we wish to report a TBHP/TBAI-promoted oxidative cyclization of *o*-acylphenols for the construction of 2-aryloxybenzofuranonefuran-3(2*H*)-ones.

Initially, the reaction of 2-acetylphenol (**1a**) with 2.0 equivalents 4-nitrophenol (**2a**) was examined in MeCN with TBAI (30 mol%) as the catalyst, and aqueous TBHP (3.0 equiv) as the oxidant at room temperature. After 24

Table 1 Optimization of the Reaction Conditions[a]



1a **2a** **3a**

Entry	Catalyst (30 mol%)	Oxidant (4.0 equiv)	Solvent	Yield (%)
1	TBAI	aq TBHP	MeCN	75 (59)[b]
2	NH_4I	aq TBHP	MeCN	55
3	KI	aq TBHP	MeCN	65
4	NIS	aq TBHP	MeCN	27
5	I_2	aq TBHP	MeCN	38
6	TBAI	aq TBHP	MeCN	58[c], 66[d]
7	TBAI	aq TBHP	EtOAc	64
8	TBAI	aq TBHP	toluene	36
9	TBAI	aq TBHP	H_2O	30
10	TBAI	H_2O_2	MeCN	28
11	TBAI	DTBP[e]	MeCN	21
12	TBAI	CHP[f]	MeCN	10
13	TBAI	–	MeCN	<10
14	–	aq TBHP	MeCN	<10

[a] The reactions were performed in a Schlenk tube with **1a** (0.5 mmol), **2a** (1.25 mmol), catalyst (30 mol%), and oxidant (4.0 equiv) in solvent (2 mL) for 16 h.
[b] The reaction temperature was 40 °C
[c] Conditions: 15 mol% TBAI were used.
[d] Conditions: 50 mol% TBAI were used.
[e] DTBP = di-*tert*-butyl peroxide.
[f] CHP = cumene hydroperoxide.

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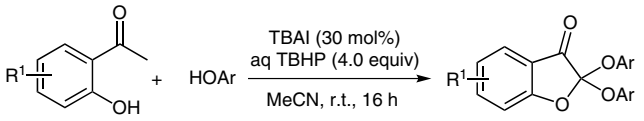
hours, a product identified as 2,2-bis(4-nitrophenoxy)-benzofuran-3(2*H*)-one (**3a**) was isolated in 55% yield. The yield of **3a** could be improved to 75% when the amount of **2a** and TBHP was increased to 2.5 equivalents and 4.0 equivalents, respectively. When the reaction was carried out at higher temperature (40 °C), only 59% yield of the product was obtained (Table 1, entry 1). Changing the iodine source to NH_4I or KI under the same conditions gave moderate yield of **3a** (Table 1, entries 2 and 3). In contrast, use of NIS[6] or I_2[7] in the reaction decreased the yields of **3a** dramatically (Table 1, entries 4 and 5). So TBAI was selected as the catalyst, and different amounts were examined but the yield of **3a** decreased (Table 1, entry 6). Changing the solvent to EtOAc, toluene, or water resulted in the formation of **3a** in lower yield (Table 1, entries 7–9). Other commercial oxidants such as H_2O_2, DTBP, and CHP were also tested and only 10–24% yields of **3a** were obtained (Table 1, entries 10–12). In the absence of TBAI or TBHP, no separable amount of product was obtained (Table 1, entries 13 and 14).

With the optimized reaction conditions established, the substrate scope was examined, and the results are summarized in Table 2.[8] Generally, electron-defect phenols, including multisubstituted phenols, underwent smooth reaction with 2-acetylphenol (**1a**) to provide the corresponding products in good yields (Table 2, entries 1–7). Remarkable steric effect was observed in this reaction. When 2-ClC_6H_4OH was used instead of 4-ClC_6H_4OH to react with **1a**, no corresponding product could be isolated (Table 2, entry 3). Phenol and electron-rich phenols were not suitable substrates to the reaction because of their instability under oxidative conditions (Table 2, entry 8). Different 2-acetylphenols with electron-donating or electron-withdrawing groups on the benzene ring reacted with 4-nitrophenol (**2a**) to give the corresponding benzofuran-3(2*H*)-ones in moderate to good yields (Table 2, entries 9–14). Heterocyclic substrate such as 1-acetyl-2-hydroxynaphthalene reacted with 4-nitrophenol (**2a**) to form the corresponding product in 60% yield (Table 2, entry15). Finally, EtOH and AcOH were also used to react with **1a** under the optimized conditions, and no significant products could be found.

Table 2 One-Pot Synthesis of 2-Aryloxybenzofuran-3(2*H*)-ones



1 **2** **3a–o**

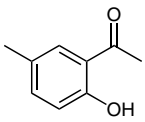
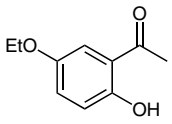
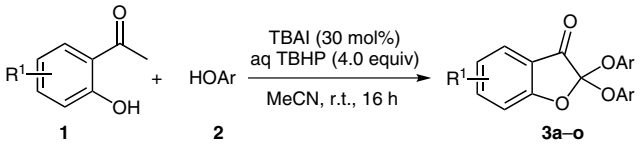
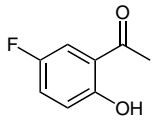
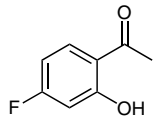
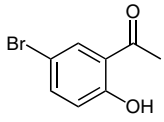
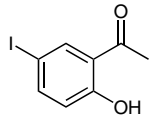
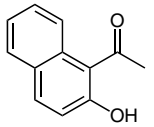
Entry	Substrate **1**	Substrate **2**	Product **3**	Yield (%)[a]
1	**1a**	4-$O_2NC_6H_4OH$	**3a**	75
2	**1a**	4-FC_6H_4OH	**3b**	65
3	**1a**	4-ClC_6H_4OH/2-ClC_6H_4OH	**3c**/**3c′**	59 0
4	**1a**	4-NCC_6H_4OH	**3d**	61
5	**1a**	4-$F_3CC_6H_4OH$	**3e**	50
6	**1a**	3,4-$Cl_2C_6H_4OH$	**3f**	68
7	**1a**	3-Me-4-$O_2NC_6H_4OH$	**3g**	60
8	**1a**	PhOH/4-MeC_6H_4OH	**3h**/**3h′**	0 0
9	 **1b**	4-$O_2NC_6H_4OH$	**3i**	62
10	 **1c**	4-$O_2NC_6H_4OH$	**3j**	60

Table 2 One-Pot Synthesis of 2-Aryloxybenzofuran-3(2*H*)-ones (continued)

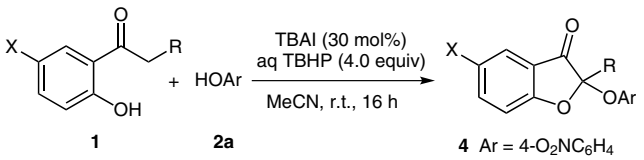


1 **2** **3a–o**

Entry	Substrate **1**	Substrate **2**	Product **3**	Yield (%)[a]
11	 **1d**	4-$O_2NC_6H_4OH$	**3k**	69
12	 **1e**	4-$O_2NC_6H_4OH$	**3l**	77
13	 **1f**	4-$O_2NC_6H_4OH$	**3m**	70
14	 **1g**	4-$O_2NC_6H_4OH$	**3n**	69
15	 **1h**	4-$O_2NC_6H_4OH$	**3o**	60

[a] Isolated yield.

Subsequently, reactivity of 2-propionylphenol (**1i**) with 4-nitrophenol (**2a**) under the optimized conditions was also examined, and 2-methyl-2-(4-nitrophenoxy)benzofuran-3(2*H*)-one (**4a**) was obtained as the major product in excellent yield up to 90%. When 2-butyrylphenol (**1j**) was employed to the reaction, the corresponding product **4b** was obtained in 72% yield (Scheme 1).



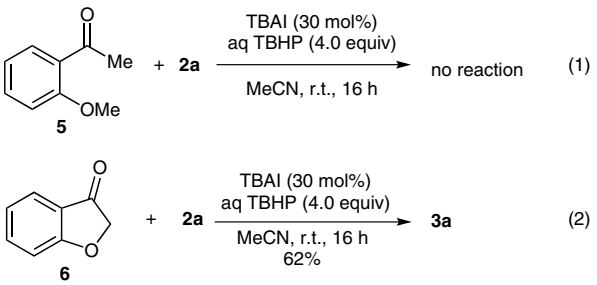
1 **2a** **4** Ar = 4-$O_2NC_6H_4$

1i X = H, R = Me
1j X = F, R = Et

4a X = H, R = Me, 90%
4b X = F, R = Et, 72%

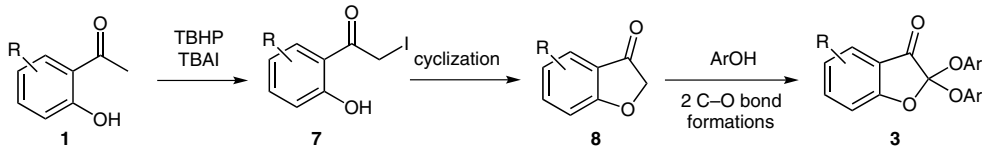
Scheme 1 Reaction of 2-propionylphenol (**1i**) and 2-butyrylphenol (**1j**) with 4-nitrophenol (**2a**)

To gain insights into the reaction mechanism, control experiments were carried, out and the results are listed below (Scheme 2). The reaction of 2-acetylanisole (**5**) with 2.0 equivalents 4-nitrophenol (**2a**) was examined under the optimized reaction conditions and no reaction occurred (Scheme 2, eq. 1), which indicated that intermolecular C–O bond formation might not be the first step of the reaction procedure, and the reaction perhaps started from an intramolecular cyclization reaction. Then benzofuran-3-(2*H*)-one (**6**) was used to react with **2a** under the same



5 **6**

Scheme 2 Control experiments



Scheme 3 Proposed pathway

conditions, **3a** could be isolated in 62% yield (Scheme 2, eq. 2).

These results suggested that benzofuran-3-(2*H*)-one (**8**) might be the crucial intermediate of the reaction, which was generated from **1** via sequence iodonation–cyclization reaction. Then **8** was converted into the final product **3** through two iodonation–C–O bond formation processes (Scheme 3). More details of the mechanism still need further investigation.

In summary, we have developed a one-pot method for the synthesis of 2-aryloxybenzofuran-3(2*H*)-ones from *o*-acylphenols and phenols under TBHP/TBAI-catalyzed conditions. The procedure was easy to handle and various 2-aryloxybenzofuran-3(2*H*)-ones have been synthesized by such a strategy. Investigation for the details of the reaction mechanism is still in progress in our lab.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are synthesis and characterization data and copies of the ^{1}H and ^{13}C NMR spectra.

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(8) **Typical Experimental Procedure for the Synthesis of 2,2-Bis(4-nitrophenoxy)benzofuran-3(2*H*)-one (3a)**
In a 15 mL reaction tube a mixture of 2-acetylphenol (**1a**, 68 mg, 0.5 mmol), 4-nitrophenol (**2a**, 174 mg, 1.25 mmol), *t*-BuOOH (70% in H_2O, 2 mmol), TBAI (55 mg, 0.15 mol) in MeCN (2.0 mL) was stirred at r.t. under air for 16 h, until complete consumption of starting material as monitored by TLC. After the reaction was finished, the mixture was quenched with sat. $Na_2S_2O_3$ solution, then extracted with EtOAc, dried over anhydrous Na_2SO_4, and evaporated in vacuum. The residue was purified by flash column chromatography on silica gel (PE–EtOAc, 8:1) to give the product **3a**.

