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Iodine(III)-Mediated Tandem Acetoxylation−Cyclization of *o*-Acyl Phenols for the Facile Construction of α-Acetoxy Benzofuranones

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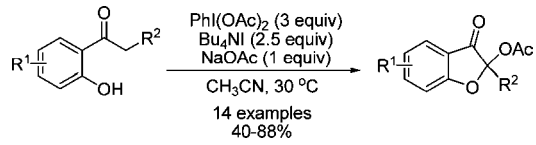
ABSTRACT



An efficient tandem acetoxylation−cyclization of *o*-acylphenols mediated by the combination of iodobenzene diacetate with tetrabutylammonium iodide provides a new convenient and useful route to α-acetoxy benzofuranones.

In the past decades, a variety of organic transformations have been shown to be mediated by the hypervalent iodine compounds.[1] In addition to their superb oxidizing properties, a remarkable feature of the organic iodine(III) compounds is their capability, like transition metals, to undergo ligand exchange and reductive elimination. This activity has been utilized to induce carbon−carbon, carbon−heteroatom, or hetero−heteroatom bond formations to construct various carbon- and heterocycles.[2] Benzofuranones (coumaranones) are important structural components of many medicinally and biologically active natural and unnatural substances.[3,4] The general synthetic pathways for the preparation of benzofuranone derivatives have involved multistep procedures or relatively harsh reaction conditions.[5] Consequently, it is desirable to search new efficient methods for the construction of benzofuranone derivatives. As part of a program aimed at developing synthetic application of hypervalent iodine compounds,[6] we have demonstrated the efficiency of the iodine(III)-induced oxidative cyclizations for the preparation of functionalized aziridines,[6b] cyclopropanes,[6d] and oxetanes.[6h] With the aim of extending this approach, we investigated the oxidative cyclization of *o*-acyl phenols.

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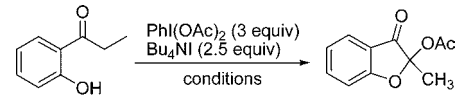
It is well-known that phenols are ready to undergo the oxidative dearomatization to yield quinones in the presence of hypervalent iodine compounds.[7] Meanwhile, Moriarty and Prakash reported the oxidation of *o*-hydroxyacetophenones to form coumaranones using $PhI(OAc)_2$ and KOH in MeOH.[5a] Interestingly, in our initial experiment with *o*-propionylphenol **1a**, which was carried out in CH_3CN at 30 °C with 2 equiv of $PhI(OAc)_2$ and 1 equiv of Bu_4NI, we did not observe the oxidative dearomatization of the phenol ring and the formation of 2-methylbenzofuranone **3**, but a product, which was identified as 2-methyl-2-acetoxybenzofuranone **2a**, was isolated in 56% yield.

Motivated by the synthetic potential of the possible method, the reaction was further optimized by examining various reaction conditions (Table 1). When 3 equiv of $PhI(OAc)_2$ and 2.5 equiv of Bu_4NI were utilized, substrate**1a** was consumed after 3 h and the yield of **2a** was improved to 71% (Table 1, entry 1). Some unidentifiable polar compounds were obtained as the byproducts. In the control experiment without Bu_4NI, no **2a** was formed. Substrate **1a** was recovered in 74% yield, and the same byproducts were detected. CH_3CN, CH_2Cl_2, THF, toluene, EtOAc, and DMF are good solvents, while alcohols are not (Table 1, entries 1−9). When the reaction was carried out in MeOH or *t*-BuOH, no 2-methyl-2-acetoxybenzofuranone **2a** or 2-methylbenzofuranone **3** was formed. Meanwhile, no corresponding 2-alkoxy derivatives were isolated from the reactions. NaOAc is a useful additive (Table 1, entry 16).

To understand the reaction pathway, several control experiments were done (Scheme 1). As the countercation, tetrabutylammonium cation is crucial to the reaction. Only a trace amount of α-acetoxy benzofuranone **2a** was formed with the use of NaI or KI. When Bu_4NI was replaced by Bu_4NBr, Bu_4NCl, or Bu_4NOAc, no reaction occurred. With PhIO or $PhI(OCOCF_3)_2$ instead of $PhI(OAc)_2$, reactions were complicated and provided only a trace amount of **2a**, while some oxidative dearomatization products of substrate **1a** were isolated. It was proposed that the reaction might be mediated by AcOI or I^+, which was generated from the reaction of

Table 1. Evaluation of Reaction Conditions



1a 2a

entry	solvent	additive	time (h)	**2a** (%)[a]
1	CH_3CN		3	71
2	CH_2Cl_2		1	63
3	THF		1	63
4	toluene		2	61
5	EtOAc		3	65
6	DMF		0.5	67
7	*t*-BuOH		3	0
8	MeOH		3	0
9	H_2O		3	0
10[b]	CH_3CN		1	35
11[c]	CH_3CN		12	trace
12	CH_3CN	HOAc (2 equiv)	3	15
13	CH_3CN	K_2CO_3 (2 equiv)	1	61
14	CH_3CN	*t*-BuOK (2 equiv)	1	58
15	CH_3CN	NaOAc (2 equiv)	1	83
16	CH_3CN	NaOAc (1 equiv)	1	88
17	CH_3CN	NaOAc (3 equiv)	1	55

[a] Isolated yield based on **1a**. [b] The reaction was carried out at 60 °C. [c] The reaction was carried out at 0 °C.

$PhI(OAc)_2$ with Bu_4NI,[8] and the generation of I_2 was observed during the reaction. However, when the combination of $PhI(OAc)_2/I_2$, I_2/Bu_4NOAc, or NIS/Bu_4NOAc was used instead of $PhI(OAc)_2/Bu_4NI$, no α-acetoxybenzofuranone **2a** was obtained. When the mixture of $PhI(OAc)_2$, Bu_4NI, and NaOAc in CH_3CN was stirred at 30 °C for 3 h before the addtion of substrate **1a**, the reaction only afforded a trace amount of product **2a**.

When 1 equiv of $PhI(OAc)_2$ and 1 equiv of Bu_4NI were used, the reaction did not finish even after 12 h. While product **2a** was obtained in 11% yield, 48% of substrate **1a** was recovered, and an α-acetoxylation product **4** was isolated in 38% yield.[9] No 2-methylbenzofuranone **3** was isolated. With the use of 3 equiv of $PhI(OAc)_2$ and 2.5 equiv of Bu_4NI (Table 1, entry 1), only a trace amount of compound **4** was detected from the reaction. α-Acetoxylation product **4** could be converted into product **2a** in 10 min with treatment with the combination of $PhI(OAc)_2/Bu_4NI$ or $PhIO/Bu_4NI$ under the same conditions (Scheme 2). The combinations of $PhI(OAc)_2/I_2$ and $PhI(OAc)_2/KOH/MeOH$ were not effective in this conversion.

A plausible reaction pathway for the $PhI(OAc)_2/Bu_4NI$-mediated tandem acetoxylation−cyclization of *o*-propionylphenol is outlined in Scheme 3. The reaction of $PhI(OAc)_2$ with Bu_4NI generates a higher reactive iodine(III) species

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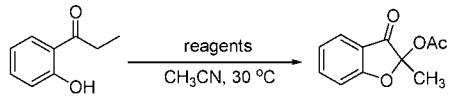
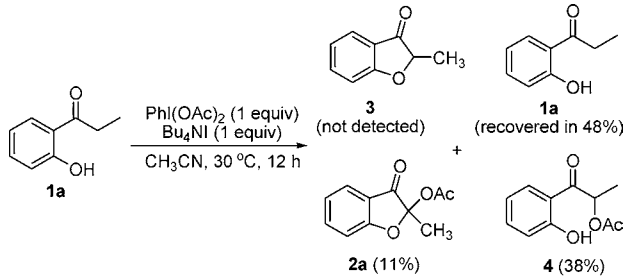
Scheme 1. Control Experiments



reagents	**2a** (%)
$PhI(OAc)_2$ (3 equiv), KI (2.5 equiv), NaOAc (1 equiv)	trace
$PhI(OAc)_2$ (3 equiv), NaI (2.5 equiv), NaOAc (1 equiv)	trace
$PhI(OAc)_2$ (3 equiv), Bu_4NBr (2.5 equiv), NaOAc (1 equiv)	0
$PhI(OAc)_2$ (3 equiv), Bu_4NCl (2.5 equiv), NaOAc (1 equiv)	0
$PhI(OAc)_2$ (3 equiv), Bu_4NOAc (3.5 equiv)	0
PhIO (3 equiv), Bu_4NI (2.5 equiv), NaOAc (2 equiv)	trace
$PhI(OCOCF_3)_2$ (3 equiv), Bu_4NI (2.5 equiv), NaOAc (2 equiv)	trace
$PhI(OAc)_2$ (3 equiv), I_2 (2.5 equiv), NaOAc (1 equiv)	0
I_2 (2 equiv), Bu_4NOAc (2 equiv), NaOAc (1 equiv)	0
NIS (2 equiv), Bu_4NOAc (2 equiv), NaOAc (1 equiv)	0

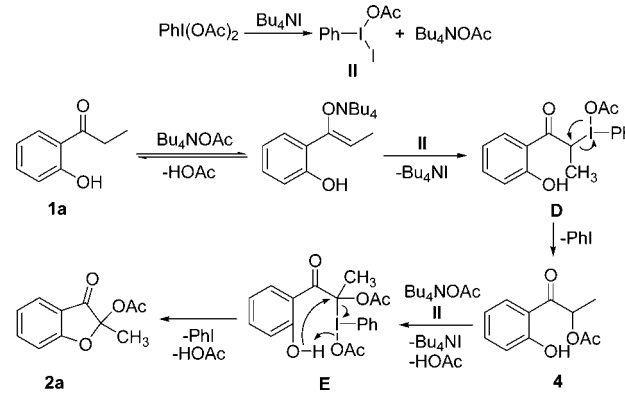
Scheme 2



reagents and conditions	**2a** (%)
$PhI(OAc)_2$ (2 equiv), Bu_4NI (2 equiv), CH_3CN, 30 °C, 10 min	85
PhIO (2 equiv), Bu_4NI (2 equiv), CH_3CN, 30 °C, 10 min	92
$PhI(OAc)_2$ (2 equiv), I_2 (2 equiv), CH_3CN, 30 °C, 1 h	0
$PhI(OAc)_2$ (2 equiv), KOH (2 equiv), CH_3OH, 30 °C, 1 h	0

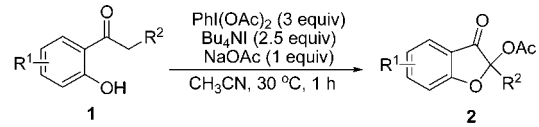
II and Bu_4NOAc, which acts as a base to deprotonate *o*-propionylphenol. The resulting enolate anion of substrate reacts with the reactive iodine(III) species **II** via a ligand exchange reaction to form an intermediate **D**, which is ready to undergo the reductive elimination to yield the α-acetoxylation product **4**. In the presence of another **II** and Bu_4NOAc, compound **4** is converted into an intermediate **E**. This is finally followed by the intramolecular nucleophilic displacement by the oxygen anion to afford α-acetoxybenzofuranone **2a** accompanied by the reductive elimination of PhI. During the reaction, acids (AcOH or HI) are generated as the byproducts. However, the existence of acids is not good for the reaction (Table 1, entry 12). When NaOAc is used as the additive, it can work as a base to eliminate the influence of acids. Moreover, the addition of NaOAc can increase the concentration of acetate anion to prompt the acetoxylation. When reaction is carried out in alcoholic solvents, $PhI(OAc)_2$ will react with alcohol to yield some other iodine(III) species to suppress the acetoxylation and cyclization reaction.[1] According to the plausible reaction pathway, a catalytic amount of Bu_4NI and 2 equiv of $PhI(OAc)_2$ are enough to complete the tandem acetoxylation−cyclization. However, the generation of the unreactive I_2, which also consumes a part of $PhI(OAc)_2$ and Bu_4NI, makes it necessary to use 3 equiv of $PhI(OAc)_2$ and 2.5 equiv of Bu_4NI.

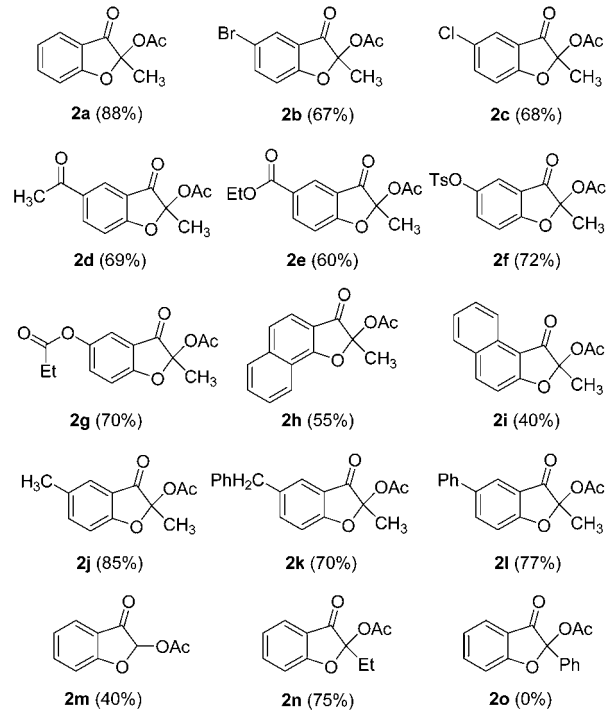
Scheme 3. Plausible Reaction Pathway for the Tandem Acetoxylation−Cyclization



The scope of this reaction was then investigated under the optimized conditions and these results are shown in Scheme 4. The reaction was found to tolerate a range of different substituents with different electronic demands on the phenol

Scheme 4. $PhI(OAc)_2$/Bu_4NI-Mediated Tandem Acetoxylation−Cyclization of *o*-Acyl Phenols





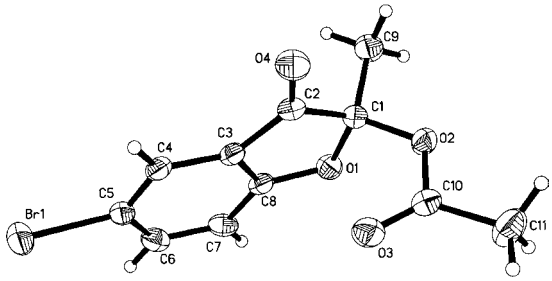
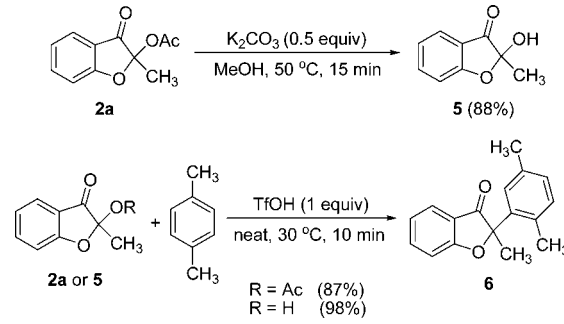


Figure 1. X-ray diffraction structure of **2b**.

rings involving electron-withdrawing and electron-donating groups. A moderate electronic substrate effect was observed. For example, reaction of *p*-methyl-*o*-propionylphenol gave rise to the corresponding product **2j** in 85% yield, while reaction of chloro- or ester-*o*-propionylphenol afforded α-acetoxybenzofuranone **2c** and **2e** in 68% or 60% yield, respectively. The yield was diminished when α- or *β*-naphthyl substrate was employed under the conditions. With respect to other *o*-acylphenols, *o*-acetyl- and butyrylphenols were also found to be suitable substrates for the tandem acetoxylation−cyclization and the desired products **2m**[10] and **2n** were generated in moderate to good yields. No corresponding α-acetoxybenzofuranone **2o** was obtained when *o*-phenylacetylphenol was utilized as the substrate. The structure of the resulting α-acetoxybenzofuranone was confirmed by the single-crystal diffraction analysis of **2b** (Figure 1).

The acetal structure of the resulting α-acetoxybenzofuranone made it ready to be converted into some other benzofuranone derivatives. We have briefly explored the conversion (Scheme 5). The treatment of product **2a** with a catalytic amount of K_2CO_3 in MeOH generated 2-hydroxyl-2-methylbenzofuranone **5** in 88% yield. In the presence of trifluoromethanesulfonic acid, products **2a** and **5** were reactive to undergo the Friedel−Crafts reaction with *p*-xylene to afford 2-(2,5-dimethylphenyl)-2-methylbenzofuranone **6** in 87% or 98% yield, respectively.

Scheme 5. Conversion of the Resulting α-Acetoxy Benzofuranone



In summary, we report here an efficient tandem acetoxylation−cyclization of *o*-acylphenols mediated by the combination of iodobenzene diacetate with tetrabutylammonium iodide. α-Acetoxybenzofuranones are synthesized in moderate to good yields. The acetal structure of the resulting α-acetoxybenzofuranone made it ready to be converted into some other benzofuranone derivatives. The scope, mechanism, and synthetic application are ongoing and will be reported in due course.

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Supporting Information Available: Experimental details and spectral data for the major products. This material is available free of charge via the Internet at http://pubs.acs.org.

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