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Aqueous Iodine(III)-Mediated Stereoselective Oxidative Cyclization for the Synthesis of Functionalized Fused Dihydrofuran Derivatives

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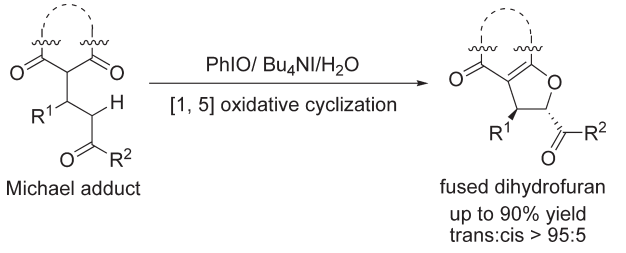
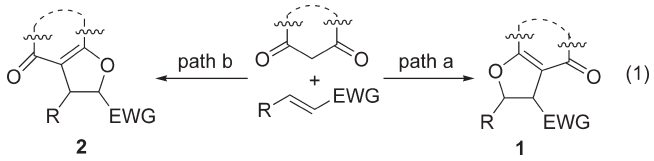


An efficient aqueous oxidative cyclization mediated by the combination of iodosobenzene with tetra-(*n*-butyl)-ammonium iodide provides a new convenient and useful route to functionalized fused dihydrofuran derivatives in moderate to excellent yields with high diastereoselectivities.

Fused dihydrofurans are frequently present as core substructures in diverse classes of natural products, which are of particular pharmaceutical value.[1] For example, coumestans, isolated from plants of the family Fabaceae, are used in folk medicine against snake poison.[2] Their important biological activities have stimulated considerable synthetic efforts.[3] The radical cyclic addition of cyclic 1,3-dicarbonyl compounds to appropriate olefins provides a versatile method for the synthesis of fused dihydrofuran derivatives.[4] When electron-poor alkenes were employed as the substrates, the radical reaction pathway resulted in the regioselective generation of product **1** with the carbon of 1,3-dicarbonyl compounds added at the α-position of electron-poor alkenes (path a, eq 1). Wang and co-workers reported a $Mn(OAc)_3$-mediated reversed regioselective radical cyclic addition (path b, eq 1).[5] However, according to the plausible reaction pathway, only 1-(pyridin-2-yl)enones were suitable substrates.



(1)

Soaring environmental awareness demands "green" chemical procedures. Hence, the development of efficient and selective chemical reactions in water with the environmentally friendly reagents via a simple procedure is desirable.[6] Oxidative cyclization is one of the most important methods for the synthesis of cyclic compounds. It can directly convert the C−H bonds into the desired C−C or C−X bonds to construct the expected cyclic compounds

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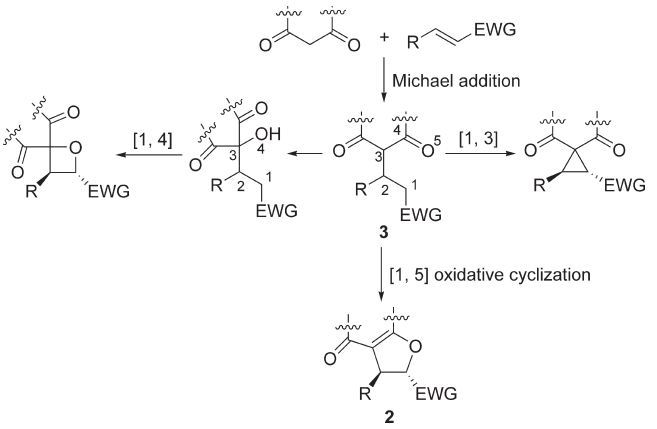
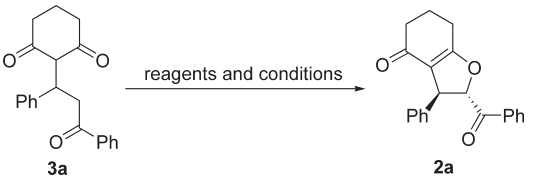
SCHEME 1



without extra chemical transformations.[7] On the other hand, as oxidants, hypervalent iodine compounds have similar or better oxidative properties than Tl(III), Hg(II), and Pb(IV) derivatives, but without the toxic and concomitant environmental problems of these heavy metal analogues. Due to their benign environmental character, ready availability, and versatility, hypervalent iodine compounds have been used extensively in organic synthesis.[8] In our previous papers,[9] we reported the formation of functionalized cyclopropanes[9d] and oxetanes[9f] from the iodine(III)-mediated oxidative cyclizations of Michael adducts of 1,3-dicarbonyl compounds with electron-poor alkenes (nitroolefins and chalcones) (Scheme 1). Here we demonstrate an efficient stereoselective construction of functionalized fused dihydrofurans via the aqueous oxidative cyclizations mediated by the combination of iodosobenzene with tetra-(*n*-butyl)ammonium iodide.

To verify our hypothesis, a set of experiments were carried out to evaluate and optimize the most efficient conditions using Michael adduct **3a**, which was prepared from the MgO-catalyzed addition of cyclohexane-1,3-dione to chalcone in 82% yield,[10] as the model substrate (Table 1). With the treatment of substrate **3a** with the combinations of $PhI(OAc)_2$/Bu_4NBr/*t*-BuOK[9b] or $PhI(OAc)_2$/KOH in MeOH,[7a] which were effectual combinations in various oxidative cyclizations, reactions did not afford any fused dihydrofuran, and the decomposition of substrate was observed (Table 1, entries 1 and 2). Interestingly, with Bu_4NI instead of Bu_4NBr, the desired product **2a** was obtained in 15% yield while the decomposition products were isolated (69% cyclohexane-1,3-dione, 74% chalcone) as the major byproducts (Table 1, entry 3). The control experiment without base did not yield product **2a** (Table 1, entry 4). In the further investigation, we discovered that the reaction could be carried out in an open-air system with water as the solvent, albeit in a lower yield (Table 1, entry 5). It is well-known that the treatment of $PhI(OAc)_2$ with aqueous KOH will lead to the generation of PhIO. To inhibit the deleterious decomposition of substrate arising from the basic conditions, PhIO was utilized to replace the combination of $PhI(OAc)_2$ and KOH, and the yield of **2a** was dramatically improved to 65% (Table 1, entry 6). A higher temperature (45 °C) resulted in a complicated reaction, while a lower temperature (15 °C) slowed the reaction and gave rise to a lower yield of **2a** (Table 1, entries 7 and 8). Although the reaction was carried out in water, no oxidative cyclization was observed with the use of KI even in the presence of a surfactant (Table 1, entries 9 and 10). The best ratio of substrate, PhIO, and Bu_4NI for the reaction was 1:1.5:1.5, with which the yield of **2a** increased to 85% (Table 1, entry 11). No corresponding cyclopropane or oxetane was isolated from the reactions.

TABLE 1. Evaluation of Reaction Conditions[a]



entry	reagents (equiv) and conditions	**2a** (%)[b]
1	$PhI(OAc)_2$ (2), KOH (2), MeOH, 2 h	0
2	$PhI(OAc)_2$ (2), Bu_4NBr (1), *t*-BuOK (2), CH_3CN, 12 h	0
3	$PhI(OAc)_2$ (2), Bu_4NI (1), *t*-BuOK (2), CH_3CN, 12 h	15
4	$PhI(OAc)_2$ (2), Bu_4NI (1), CH_3CN, 12 h	0
5	$PhI(OAc)_2$ (2), Bu_4NI (1), KOH (2), H_2O, 24 h	11
6	PhIO (2), Bu_4NI (1), H_2O, 24 h	65
7	PhIO (2), Bu_4NI (1), H_2O, 45 °C, 24 h	18
8	PhIO (2), Bu_4NI (1), H_2O, 15 °C, 36 h	43
9	PhIO (2), KI (1), H_2O, 24 h	0
10	PhIO (2), KI (1), *p*-$C_{12}H_{25}$−$C_6H_4SO_3Na$ (1), H_2O, 24 h	0
11	PhIO (1.5), Bu_4NI (1.5), H_2O, 16 h	85

[a]Reaction conditions: substrate **3a** (0.2 mmol), solvent (1 mL) at 30 °C, unless noted. [b]Isolated yield.

The scope of this reaction was then investigated under optimized conditions, and the results are summarized in Table 2. The Michael adducts of chalcone with 5,5-dimethylcyclohexane-1,3-dione (dimedone), 6-methyl-3*H*-pyran-2,4-dione, chroman-2,4-dione (4-hydroxycoumarin), and 6-fluorochroman-2,4-dione (4-hydroxy-6-fluorocoumarin) were effective substrates, and their reactions gave rise to the corresponding fused dihydrofurans in good to excellent yields (up to 90% yield). Products **2d**, **2e**, and **2f** have similar core structures with naturally occurring coumestans. When the derivative of 2*H*-indene-1,3-dione **3g** was employed as the substrate, only the decomposition of substrate was observed. Additionally, the aqueous oxidative cyclization was found to tolerate a range of groups with different electronic demands on the aromatic rings. For the substrates derived from different chalcones with an electron-donating or an electron-withdrawing substitution, reactions proceeded smoothly and afforded the corresponding products **2h**−**2p** in yields ranging from 56 to 85%. When the aryl group at R^2 was replaced by an alkyl group (substrates **3q** and **3r**), no oxidative cyclization occurred under the same conditions.

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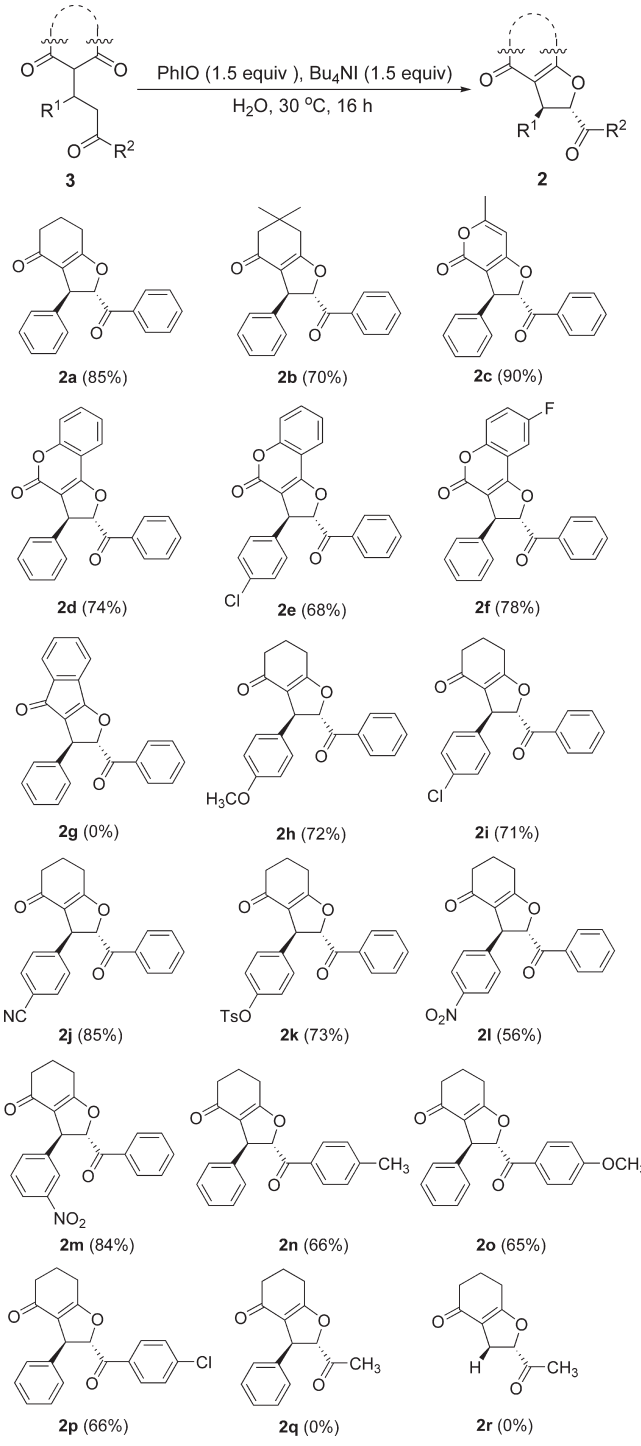
TABLE 2. Aqueous Oxidative Cyclization[a,b]



[a]Reaction conditions: substrate **3** (0.2 mmol), PhIO (0.3 mmol), Bu_4NI (0.3 mmol), H_2O (1 mL) at 30 °C for 16 h. [b]Isolated yield.

We failed in the preparation of the Michael adducts from the enones, which were derived from acetaldehyde,

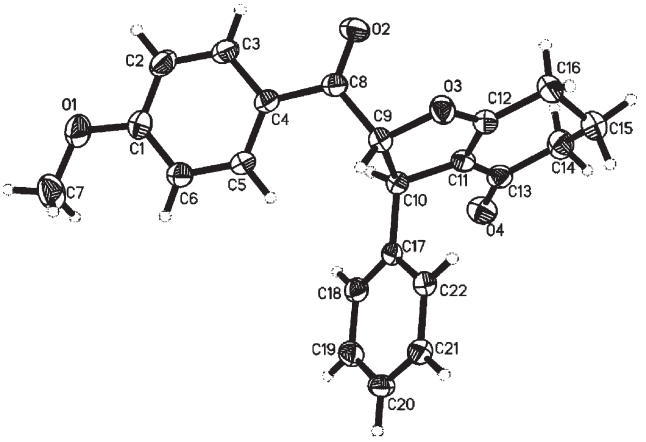
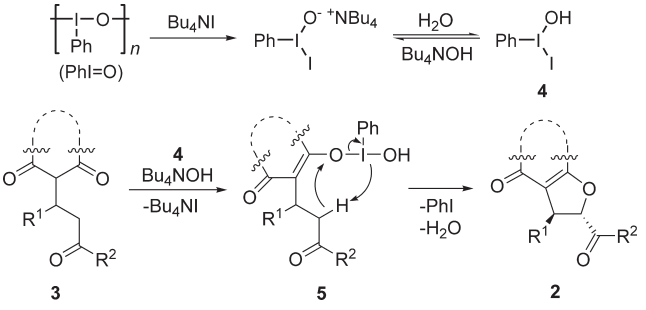


FIGURE 1. X-ray diffraction structure of **2o**.

SCHEME 2. Hypothesized Reaction Pathway



isobutyraldehyde, and cinnamaldehyde. All fused dihydrofurans were formed with a high diastereoselectivity (*trans*/*cis* > 95:5), and their structures were determined based on their ^{1}H NMR (the observed coupling constants between two methine protons were 4.6−5.2 Hz),[5,11] ^{13}C NMR, HRMS, and FT-IR spectra. The structure and the *trans* stereochemistry were further confirmed by the single-crystal diffraction analysis of product **2o** (Figure 1).

Reactions afforded PhI as the byproduct. Moreover, during the reaction, we observed the generation of iodine, which indicated that the oxidative cyclization might be mediated by I_2 or I^+. However, when the combination of PhIO/Bu_4NI was replaced by those of PhIO/I_2, I_2/Bu_4NOAc, NIS/Bu_4NOAc, and ICl/Bu_4NOAc, no dihydrofuran was formed. Additionally, no oxidative cyclization occurred with Bu_4NCl or Bu_4NBr instead of Bu_4NI. A hypothesized reaction pathway for the PhIO/Bu_4NI-mediated construction of fused dihydrofurans is shown in Scheme 2. A higher reactive iodine(III) species **4**, which is generated from the depolymerization of the polymeric iodosobenzene[12] by Bu_4NI,[13] reacts with the enolate of Michael

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adduct **3** via a ligand exchange reaction[8f,14] with the aid of the resultant Bu_4NOH to give rise to an intermediate **5**. Intermediate **5** is ready to undergo an intramolecular reductive elimination to afford fused dihydrofuran **2**.[15]

In summary, we have developed an efficient method for the construction of functionalized fused dihydrofurans via an aqueous PhIO/Bu_4NI-mediated stereoselective oxidative cyclization of Michael adducts of cyclic 1,3-dicarbonyl compounds with chalcones. The potential of this reaction system can be evaluated by its simple procedure, mild conditions, and adaptability to a wide variety of substrates. The further development of the asymmetric reactions is ongoing and will be reported in due course.

Experimental Section

Representative experimental procedure: The mixture of Michael adduct **3a** (64 mg, 0.2 mmol) and PhIO (66 mg, 0.3 mmol) in H_2O (1 mL) was treated with Bu_4NI (111 mg, 0.3 mmol). The reaction was allowed to stir at 30 °C for 16 h. Upon completion by TLC, the reaction mixture was quenched with saturated $Na_2S_2O_3$ (25 mL) and extracted by ethyl acetate (25 mL × 3). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (15% ethyl acetate in hexanes) to provide 2-benzoyl-3-phenyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one **2a** in 85% yield as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80−7.83 (m, 2 H), 7.61 (t, J = 7.3 Hz, 1 H), 7.45 (t, J = 7.3 Hz, 2 H), 7.35 (t, J = 7.3 Hz, 2 H), 7.22−7.30 (m, 3 H), 5.87 (d, J = 4.6 Hz, 1 H), 4.41 (d, J = 4.6 Hz, 1 H), 2.72 (t, J = 6.6 Hz, 2 H), 2.33 (t, J = 6.4 Hz, 2 H), 2.10−2.16 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4, 193.0, 177.4, 141.2, 134.3, 133.3, 129.1, 129.0, 128.9, 127.7, 127.4, 116.6, 91.7, 49.0, 36.9, 24.0, 21.8; IR (KBr) 2949, 1696, 1639, 1597, 1393, 1226 cm^{-1}; HRMS m/z calcd for $C_{21}H_{19}O_3$ ($[M + H]^+$) 319.1329, found 319.1327.

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Supporting Information Available: Experimental procedures, characterization data, copies of ^{1}H NMR and ^{13}C NMR of new compounds, and crystallographic data of compound **2o** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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