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Water-Tolerant *ortho*-Acylation of Phenols

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Cite This: *Org. Lett.* 2021, 23, 6594−6598 Read Online

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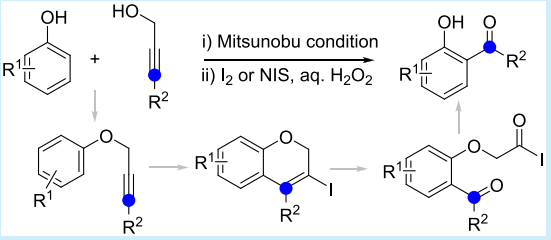
ABSTRACT: A metal-free, water-tolerant, and one-pot process for *ortho*-acylation of phenols promoted by the iodine source/hydrogen peroxide system has been developed. This transformation undergoes ether formation, iodocyclization, C−C bond cleavage, and oxidative hydrolysis in a one-step manner, which is supported by control experiments.



Phenolic compounds are prevalent in nature. Examples include lignin in plants, peptides and proteins containing tyrosine amino acid, steroids such as estrones, etc.[1] They are also featured widely in many advanced materials and pharmaceuticals and also used as chiral ligands such as BINOLs in asymmetric synthesis.[2] Therefore, the ability to selectively functionalize phenols will lead to the discovery of new drugs, materials, chiral ligands, new turbine bioconjugation methods, etc.[3] Among them, traditional Friedel−Crafts acylation or Fries rearrangement of esters derived from phenols[4] (Figure 1b) is regarded as a very useful method for the synthesis of *ortho*-acylphenols, which are found in many natural products and drugs as bioactive cores[5] (Figure 1a). Howeve, it is still difficult to realize *ortho*-acylation of complex phenolic molecules or phenols with active or acid-sensitive groups by traditional methods. Recently, Rh/Cu catalyzed *ortho*-acylation of *N*-phenoxyacetamide with alkyne has also been reported as an alternative method[6] (Figure 1b).

On the other hand, the environmentally benign iodine source/hydrogen peroxide catalytic system was found to be very effective for some oxidative couplings.[7−11] Among them, enantioselective cycloetherification by Ishihara and co-workers,[8] diamination of styrene,[9] cross-dehydrogenative couplings,[10] and our reported α-amination of aldehydes[11] are regarded as representative examples. With our continuous efforts to explore these green aspects of organic transformations, we concentrate on the development of a novel and efficient chemical process to realize the *ortho*-acylation of phenols under the conditions of a metal-free, water-tolerant, and environmentally friendly oxidant (O_2, aqueous H_2O_2) in a one-step manner by employing simple and readily available substrates as starting materials.

For this goal, intramolecular cascade transformations into *ortho*-acylphenol skeletons starting from propargyl aryl ether is an important and challenging task because metal-free cleavage and reassembly of the unsymmetrical C−C triple bond[12] and metal-free cross-coupling at the *ortho* position of phenols[13] are

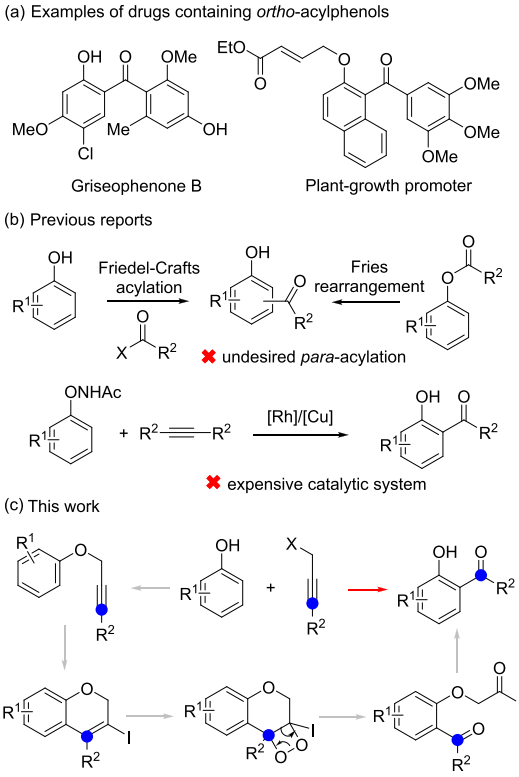


Figure 1. Strategy for metal-free, one-pot *ortho*-acylation of phenols.

Received: August 3, 2021
Published: August 11, 2021

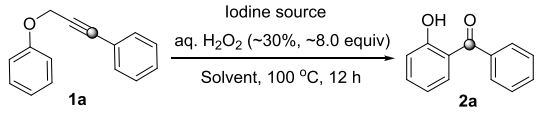
https://doi.org/10.1021/acs.orglett.1c02583
Org. Lett. 2021, 23, 6594−6598

rarely achieved. In this context, we envisage that a cascade reaction involving iodocyclization, C−C bond cleavage, and oxidative hydrolysis in the oxidative system of iodine source/hydrogen peroxide may be feasible (Figure 1c). In this process, aqueous hydrogen peroxide serves as a green oxidant and oxygen source.

In this paper, we report a novel, metal-free, and water-tolerant method for the synthesis of *ortho*-acylphenols promoted by the iodine source/hydrogen peroxide system. This transformation smoothly proceeds through ether formation, iodocyclization, C−C bond cleavage, and oxidative hydrolysis in a one-step manner. In addition, control experiments led to a possible mechanism.

The iodine source/hydrogen peroxide catalytic system was examined for the reaction by selecting propargyl aryl ether **1a** as a model substrate (Table 1). Our preliminary study was

Table 1. Optimization of the Reaction Conditions[a]



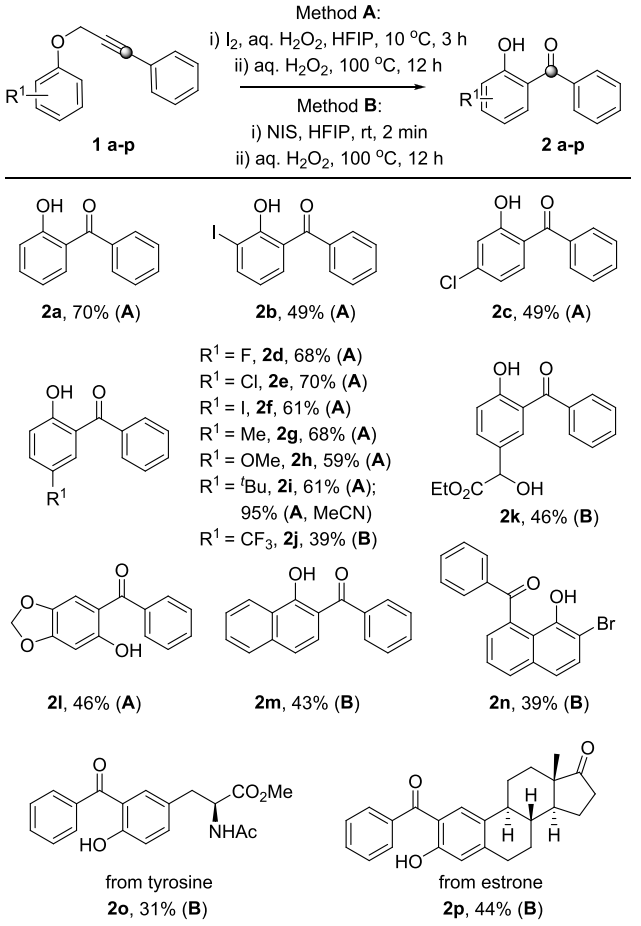
entry	iodine source (equiv)	solvent	yield (%)[b]
1	—	HFIP	0
2	NaI (0.6)	HFIP	trace
3	I_2 (0.3)	HFIP	29
4	I_2 (0.4)	HFIP	47
5[c]	I_2 (0.4)	HFIP	trace
6	I_2 (0.6)	HFIP	46
7	NIS (0.8)	HFIP	42
8[d]	I_2 (0.4)	HFIP	39
9	I_2 (0.4)	MeCN	38
10	I_2 (0.4)	1,4-dioxane	0
11	I_2 (0.4)	^{t}BuOH	0
12	I_2 (0.4)	DMSO	0
13[e]	**I_2 (0.4)**	**HFIP**	**70**
14[e]	I_2 (0.4)	$MeNO_2$	64
15[f]	**NIS (1.0)**	**HFIP**	**67**

[a]The reaction was carried out with propargyl aryl ether **1a** (0.2 mmol), iodine source, aqueous H_2O_2 (~163.4 μL, ~30%, ~8.0 equiv) in solvent (0.5 mL) under air atmosphere at 100 °C for 12 h. [b]Isolated yields. [c]80 °C. [d]*tert*-Butyl hydroperoxide (~65% solution in water, ~8.0 equiv). [e]Method **A**: After **1a** (0.2 mmol), iodine (0.4 equiv), and aq. H_2O_2 (~40.8 μL, ~30%, ~2.0 equiv) in HFIP (0.5 mL) were stirred at 10 °C for 3 h, additional aq. H_2O_2 (~122.6 μL, ~30%, ~6.0 equiv) was then added and stirred at 100 °C for 12 h. [f]Method **B**: **1a** (0.2 mmol) and NIS (1.0 equiv) in HFIP (0.5 mL) were stirred at rt for 2 min, and aq. H_2O_2 (~81.6 μL, ~30%, ~4.0 equiv) was then added and stirred at 100 °C for 12 h.

carried out by varying the iodine source with aqueous H_2O_2 (~30%, ~8.0 equiv) as the oxidant and oxygen source in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) under an air atmosphere at 100 °C for 12 h. As shown in Table 1, no target product was detected without any iodine source (Table 1, entry 1). When sodium iodide was used for the reaction, only a trace of product could be observed (Table 1, entry 2). Gratifyingly, molecular iodine could provide *ortho*-acylphenol **2a** in a yield of 29% (Table 1, entry 3). Intriguingly, when the amount of iodine was changed to 0.4 equiv, the yield was increased to 47% (Table 1, entry 4). However, the yield was not further improved by increasing the catalytic quantity of iodine (Table 1, entry 6). *N*-Iodosuccinimide (NIS) was also found to be effective for this transformation, and the desired product was afforded in 42% yield while 0.8 equiv of NIS was used (Table 1, entry 7). Additionally, *tert*-butyl hydroperoxide (~65% solution in water) took part in this reaction and the desired product **2a** could be obtained in 39% yield (Table 1, entry 8; see SI for other oxidants). Then, the effects of solvents on the reaction were evaluated. As revealed in Table 1, entries 9−12, HFIP had the better effect than other solvents, such as acetonitrile, 1,4-dioxane, and *tert*-butanol (see SI for other solvents). Finally, considering that aqueous hydrogen peroxide played the role of a green oxidant, an oxygen source, and an aqueous medium in the reaction, further investigation into the way of adding it to the reaction was attempted. To our delight, the yield could be increased to 70% with Method **A** (Table 1, entry 13) or 67% with Method **B** (Table 1, entry 15).

Subsequently, the scope of different phenolic structures was investigated by using the optimized Method **A** or **B** as shown in Scheme 1. The halogen functionality at the *ortho*-, *meta*-, or

Scheme 1. Scope of Different Phenolic Structures[a,b]



[a]Reactions were carried out with Method **A** or **B**. [b]Yields of the isolated products are given.

para-positions of phenol proceeded smoothly with Method **A**, and the corresponding products **2b−f** were afforded in 49%−70% yields. A variety of substrates **1d−j** bearing electron-donating or weak electron-withdrawing *para*-substituents such as Me, OMe, ^{t}Bu, and CF_3 were also suitable for this transformation, providing the desired products **2d−j** in moderate to good yields. *para*-Hydroxymandelic acid and

https://doi.org/10.1021/acs.orglett.1c02583
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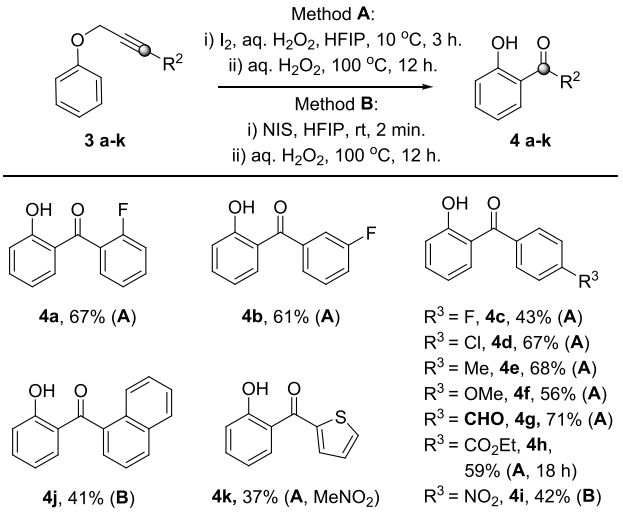
sesamol are important intermediates for the preparation of antihypertensive drugs. Consequently, *para*-hydroxymandelic ester **1k** and sesamol **1l** were used for the reaction and it is interesting that these mild conditions showed good tolerance to free active hydroxyl and diether groups. For an aromatic fused ring, 1-naphthol derivative **1m** was selected as a representative example for this process, and 2-benzoyl-1-naphthol **2m** was obtained in 43% yield. In contrast, when 2-bromo-1-naphthol derivative **1n** was used for this reaction, the acylation only occurred at the C-8 position while no C-2 or C-4 acylated product was observed, which also supported the existence of a cyclized intermediate. Late-stage diversification of drugs or natural products containing phenolic structures is further studied. The reaction with the substrates **1o−p** separately derived from tyrosine and estrone were attempted with Method **B**. Luckily, potential acylation drugs **2o−p** were isolated with yields of 31%−44%. Additionally, propargyl aryl ether derived from *N*-Boc-tyrosine or the corresponding iodocyclized intermediate was also attempted for this transformation. Unfortunately, no target product was obtained.

Next, we explored the scope of aryl alkyne motifs as presented in Scheme 2. First, the effect of a fluorine substituent

Scheme 2. Scope of Aryl Alkyne Motifs[a,b]

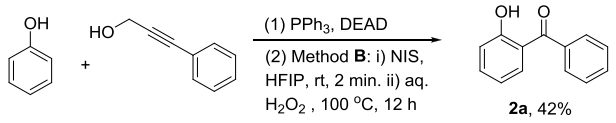


[a]Reactions were carried out with Method **A** or **B**. [b]Yields of the isolated products are given.

at different positions of the aromatic ring was examined, and the results showed that the order of acylation reactivity is *ortho* (**3a**, 67%) > *meta* (**3b**, 61%) > *para* (**3c**, 43%) when Method **A** was used. Then, a series of aryl alkynes with various functional groups at the *para* position, such as, chloro, methyl, methoxy, formyl, ester, and nitro groups, were evaluated, giving the corresponding acylated products **4d−i** in 42%−71% yields. It is noteworthy that an easily oxidized aldehyde group is compatible to the mild catalytic system. Likewise, the substrates bearing other (hetero)aromatic alkyne motifs, such as naphthyl and thienyl groups, were also competent in the transformation, delivering the target products **4j−k** in 37%−41% yields.

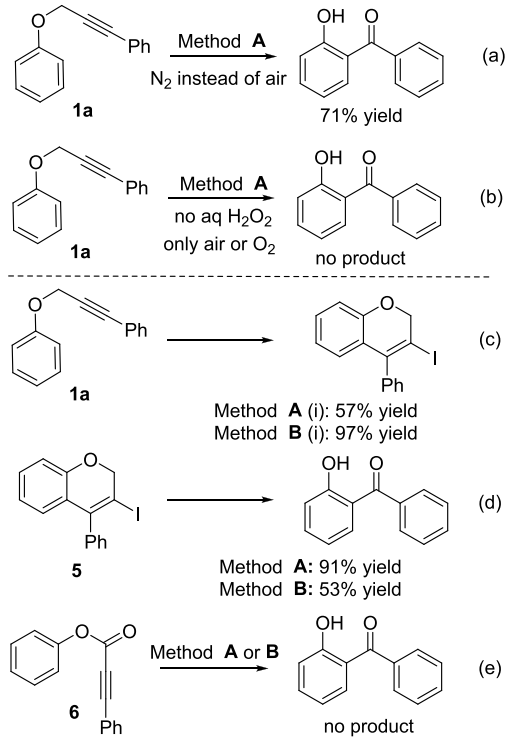
After the identification of the catalytic system and expanding the scope of propargyl aryl ether, we next explored the feasibility of metal-free, one-pot acylation reaction of phenol with alkynol, which was prepared from phenylacetylene and paraformaldehyde.[14] Phenol and 3-phenylprop-2-yn-1-ol were chosen as the starting materials. After the successive operation of the Mitsunobu reaction[15] and Method **B** without column chromatography separation, it is gratifying that *ortho*-acylphenol **2a** was isolated in 42% yield (Scheme 3).

Scheme 3. Metal-Free, One-Pot Acylation of Phenol with 3-Phenylprop-2-yn-1-ol



To clarify the reaction process for metal-free *ortho*-acylation of phenols with alkynol, several control experiments were carried out as revealed in Scheme 4. First, using a N_2

Scheme 4. Control Experiments



atmosphere instead of air, the model reaction was performed smoothly with Method **A** [Scheme 4, eq (a)]. In contrast, no reaction occurred by using only air or O_2 as the oxidant for the model reaction without aqueous H_2O_2 [Scheme 4, eq (b)]. Thus, hydrogen peroxide is the active oxidant in the reaction. Next, 3-iodo-4-phenyl-2*H*-benzopyran **5** can be produced through the iodocyclization of propargyl phenyl ether **1a** under Method **A** (i) or **B** (i) [Scheme 4, eq (c)]. Then, the cyclized intermediate **5** was subjected to Method **A** or **B** [Scheme 4, eq (d)] and the desired product **2a** was isolated in 91% or 53% yield. The results supported the involvement of iodocyclization and oxidative cleavage in the acylation reaction. In addition, phenyl 3-phenylpropiolate **6** can not afford the acylated product **2a** [Scheme 4, eq (e)]. This shows that iodocyclization is more likely to occur in oxidative hydrolysis in the iodine/hydrogen peroxide system.

https://doi.org/10.1021/acs.orglett.1c02583
Org. Lett. 2021, 23, 6594−6598

On account of control experiments and related literature reports,[16] a mechanistic hypothesis about metal-free acylation of phenols starting from propargyl aryl ether **1** or **3** was proposed as shown in Figure 2. First, electrophilic hypoiodite

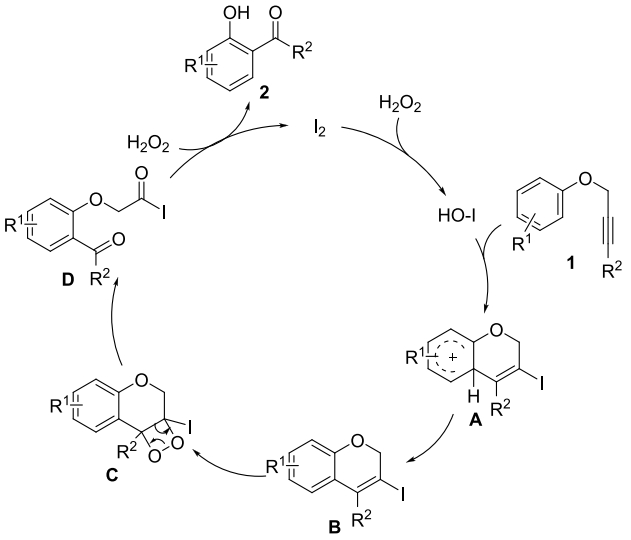


Figure 2. Mechanistic hypothesis.

is *in situ* generated by molecular iodine with hydrogen peroxide, which reacts with propargyl aryl ether **1** or **3** through intramolecular iodoarylation reaction to afford benzofused heterocycle **B**. Then, under the assistance of hydrogen peroxide the oxidative cleavage of the iodinated double bond occurs through the dioxetane intermediate **C**. Finally, the oxidative hydrolysis of aryl ether **D** activated by an electron-withdrawing group provides the acylation product **2** or **4**.

In summary, a metal-free, water-tolerant, and one-pot acylation reaction of phenols through an oxidative cleavage process of a C−C triple bond has been developed by using the iodine source/hydrogen peroxide system. Control experiments supported this one-pot transformation that involved a Mitsunobu reaction, iodocyclization, C−C bond cleavage, and oxidative hydrolysis. Further expansion of the metal-free, one-pot method and practical applications, especially in the modification of drugs and peptides, is underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02583.

Synthetic procedures, mechanistic studies, and NMR data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge Northwestern Polytechnical University, the Fundamental Research Funds for the Central Universities (D5000210701), Tier 1 Grant M4012045.110 (RG12/18-S) from the Ministry of Education of Singapore, Nanjing Tech University, and Nanyang Technological University for the generous financial support.

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