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Synthesis of 4-Chloroisocoumarins via Intramolecular Halolactonization of *o*-Alkynylbenzoates: $PhICl_2$-Mediated C−O/C−Cl Bond Formation

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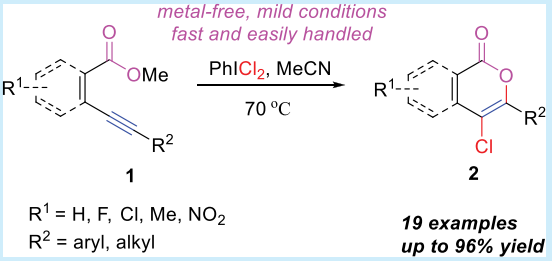
Supporting Information

ABSTRACT: A series of 4-chloroisocoumarins were conveniently synthesized from *o*-alkynylbenzoates via $PhICl_2$-mediated intramolecular cyclization under metal-free conditions. $PhICl_2$ plays the role of both the oxidant and the chlorine source to enable oxidative C−O bond formation and introduction of the chlorine atom. The utility and practicability of this protocol have been exemplified by virtue of mild reaction conditions, high-yielding products, simplified purification, and gram-scale synthesis.



Isocoumarins, one class of privileged heterocyclic scaffolds, are featured as the core structures of many naturally occurring compounds.[1−6] A large number of natural products containing the isocoumarin skeleton have been found to display a broad spectrum of biological activities.[7−16] For example, compound **I** can be used as a potent irreversible inhibitor of blood coagulation enzymes,[12] 3-(2-bromoethoxy)-isocoumarin (**II**) has been investigated as an inhibitor of human leukocyte elastase,[13] cercophorin A (**III**) was studied as an antifungal agent,[14] LGK 2 (**IV**) has been used as a β-amyloid peptide production inhibitor,[15] and 7-hydroxy-3-(4-hydroxyphenyl)isocoumarin (**V**) was investigated as a selective estrogen receptor β ligand.[16] Because of the pharmaceutical importance of isocoumarin compounds, there has been growing interest in the development of efficient strategies for their synthesis (Figure 1).[17−30]

Among the synthetic approaches, the synthesis of 4-haloisocoumarins has received considerable attention as these molecules possess interesting biological activities and the presence of a halogen atom at position 4 allows for further functionalization.[31−45] The predominant synthetic method used for the generation of 4-haloisocoumarins is the electrophilic cyclization of *o*-alkynylbenzoates using various electrophiles, including Br_2,[31,34] I_2,[32,35−37] ICl,[35−37,42] NBS,[43] and NIS.[45] However, these methods are applicable only to the preparation of 4-iodo/bromoisocoumarins, and the synthesis of 4-chloroisocoumarins relies predominantly on the application of transition metal-mediated approaches.[33,35,38−40,44] For example, Lisowski described a Cy_2NH·HCl-promoted cyclization of *o*-alkynylbenzoates with $CuCl_2$ to give 4-chloroisocoumarins (Scheme 1, method a).[35] Similarly, Miyata reported the halocyclization of *o*-alkynylbenzoates using $CuCl_2$/NCS (Scheme 1, method b).[39] However, these methods suffer from the inevitable use of a stoichiometric amount of the transition metal. Most recently, Li developed an alternative route to the construction of 4-chloroisocoumarins from phenyl 2-(2-phenylethynyl)benzoate using TBAC and oxone.[41] However, only one example was given, and the versatility and generality of this electrophilic chlorocyclization approach were unexplored. Furthermore, when the most simple ester substrate, methyl *o*-alkynylbenzoate, was subjected to the standard conditions, a diketone, rather than the 4-chloroisocoumarin product, was obtained. In this work, we reported an alternative approach for convenient and efficient construction of the biologically interesting 4-chloroisocoumarin skeleton using $PhICl_2$ as both the oxidant and the chlorine source.

(Dichloroiodo)arenes, hypervalent iodine reagents widely used in organic synthesis, are often used as a replacement for gaseous chlorine, which is a toxic gas and is hard to handle in

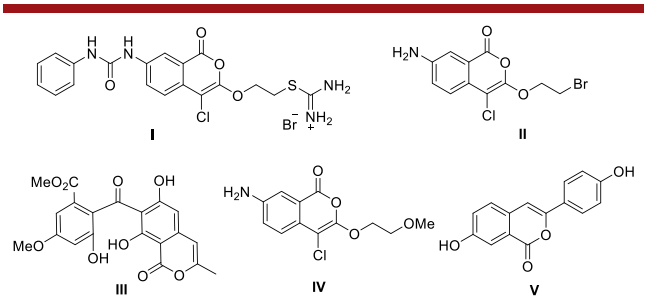


Figure 1. Representative naturally occurring and pharmaceutically active isocoumarins.

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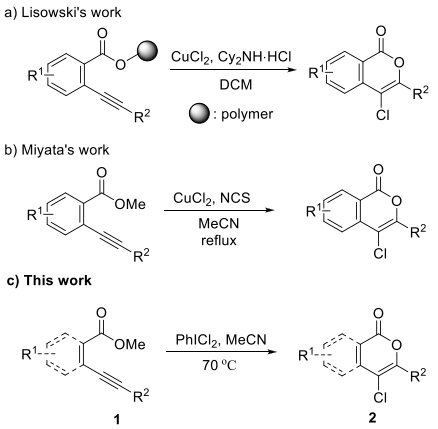
Scheme 1. Existing Strategies for the Synthesis of 4-Chloroisocoumarins

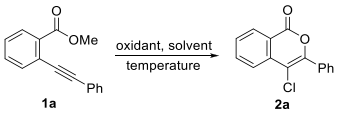


most cases. Because of desirable properties such as their ease of handling, ready availability, nontoxicity, and environmentally benign properties, (dichloroiodo)arenes have found broad synthetic application as reagents for both chlorination and oxidation reactions.[46−50] For example, (dichloroiodo)arenes have been applied to the typical chlorination of alkanes or alkenes, substitutive chlorination at the sp^3 carbon of various organic substrates, including alkanes, ethers, esters, thioethers, ketones, and sulfoxides, and chlorination of a variety of organic compounds containing heteroatoms such as sulfur, phosphorus, selenium, arsenic, antimony, and some metals.[47] However, to the best of our knowledge, the application of (dichloroiodo)benzene ($PhICl_2$) to the synthesis of chloro-substituted isocoumarins has not yet been explored. In this regard, we were interested in determining whether *o*-alkynylbenzoates could be converted to 4-chloroisocoumarins via a $PhICl_2$-mediated intramolecular cyclization/chlorination process.

At the outset of the study, 2-alkynoate **1a** was used as a model substrate to test the feasibility of the proposed transformation. No reaction occurred when substrate **1a** was treated with 1.2 equiv of $PhICl_2$ in CH_3CN at room temperature. To our delight, the cyclization successfully produced **2a** in 92% yield when the reaction temperature was increased to 60 °C (Table 1, entry 2). Solvent screening showed that CH_3CN was the most favorable solvent in comparison to DCE, ethyl acetate, DMF, toluene, dioxane, $CHCl_3$, and THF (Table 1, entries 2−9, respectively). As a result of the adjustment of the temperature from 60 to 70 °C, the yield of product **2a** was improved from 92% to 96%, while further increasing the temperature to 80 °C was not beneficial to the outcome of the reaction (Table 1, entries 2, 10, and 11). Furthermore, we also investigated the reaction using PIFA or PIDA as the oxidant and $FeCl_3$ as a chlorine source. To our disappointment, neither of these reagents was found to be superior to the current approach using $PhICl_2$ as both the oxidant and the chlorine source. NCS was also investigated and was found not to mediate the reaction, which indicated that $PhICl_2$ cannot be replaced by the commonly used NCS for this transformation. On the basis of the screening results, optimized conditions were concluded to be 1.0 equiv of 2-alkynoate **1a** and 1.2 equiv of $PhICl_2$ in CH_3CN at 70 °C (Table 1, entry 10).

Under the optimized conditions, a series of 4-chloroisocoumarin derivatives were prepared by this newly established

Table 1. Optimization of Reaction Conditions[a]



entry	oxidant	solvent	temp (°C)	yield (%)[b]
1	$PhICl_2$	CH_3CN	rt	ND
2	$PhICl_2$	CH_3CN	60	92
3	$PhICl_2$	DCE	60	88
4	$PhICl_2$	EtOAc	60	ND
5	$PhICl_2$	THF	60	ND
6	$PhICl_2$	DMF	60	ND
7	$PhICl_2$	toluene	60	<5
8	$PhICl_2$	dioxane	60	ND
9	$PhICl_2$	$CHCl_3$	60	10
10	$PhICl_2$	CH_3CN	70	96
11	$PhICl_2$	CH_3CN	80	90
12	PIDA[c]	CH_3CN	70	36
13	PIFA[c]	CH_3CN	70	33
14	NCS	CH_3CN	70	ND

[a]Reaction conditions: **1a** (0.5 mmol) and oxidant (0.6 mmol) in solvent (5 mL) for 15 min. [b]Isolated yields. [c]Using $FeCl_3$ (0.6 mmol) as the chlorine source.

approach. Substituent effects of R^1 and R^2 were studied to probe the scope and limitations of this method. Substrates bearing either an electron-withdrawing group (R^1 = F, Cl, or NO_2) or an electron-donating group (R^1 = Me) at position 5 were converted to the desired cyclized products in satisfactory to excellent yields (Scheme 2, **2b−e**). It is worth noting that reaction of the substrate when R^1 is the strongly electron-withdrawing NO_2 group required a larger dosage of oxidant and a longer reaction time (Scheme 2, **2b**). Likewise, substrates bearing either a F or Cl substituent at position 4 gave the corresponding products in satisfactory yields (Scheme 2, **2f** and **2g**).

Investigation of the substituent effect of the alkyne motif showed that the reactions of diversely substituted phenyl-, 2-naphthyl-, 2-thienyl, and alkyl-substituted alkynoates proceeded smoothly to afford the corresponding 4-chloroisocoumarins **2h−r** in 41−96% yields. For instance, substrates with different phenyl-substituted R^2 groups were well tolerated and generated the corresponding products **2h−n** in excellent yields, regardless of the nature of the substituents on the phenyl ring. Meanwhile, the reaction of 2-naphthyl- and 2-thienyl-substituted substrates also gave the corresponding isocoumarins **2o** and **2p** in 84% and 83% yields, respectively. Most strikingly, it was found that the method could be further extended to the preparation of 3-alkyl-substituted cyclized products such as 3-*tert*-butyl 4-chloroisocoumarin **2q** and 3-cyclopropyl 4-chloroisocoumarin **2r**. Furthermore, the method could also be applied to the cyclization/chlorination of (*Z*)-methyl 5-phenylpent-2-en-4-ynoate, with the desired product **2s** achieved in satisfactory yield. Unfortunately, the reaction involving a substrate bearing an *n*-butyl R^2 group gave a complex mixture, and no desired cyclized product was isolated and/or observed (Scheme 2, **2t**). It is noteworthy that most of the reactions proceeded rapidly and were completed within 15 min. Furthermore, the desired products could be crystallized from the reaction mixture in relatively high yields, which dramatically simplified purification.

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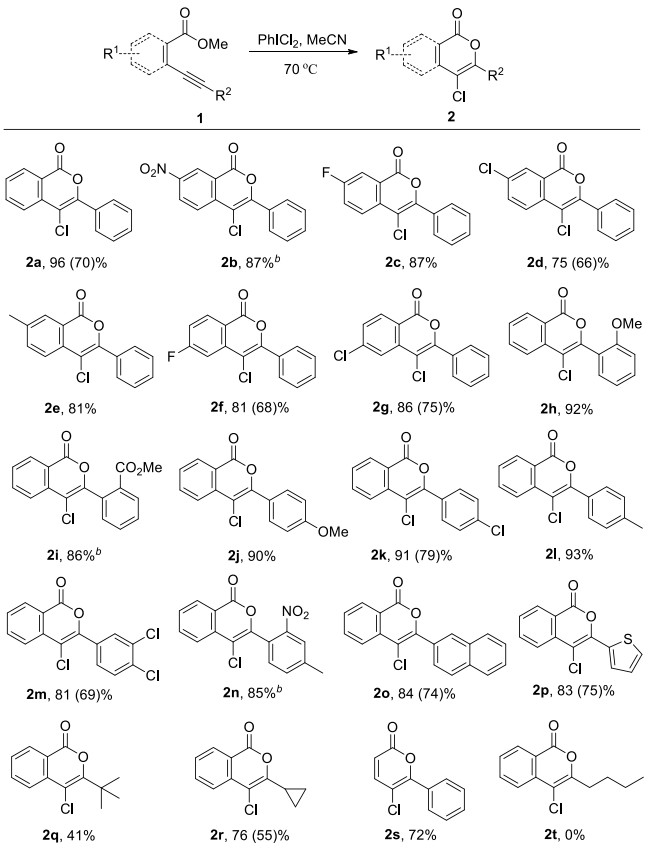
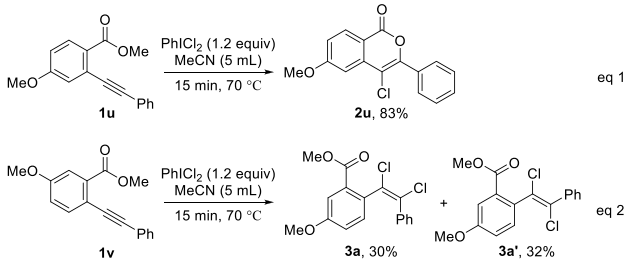
Scheme 2. Halocyclization of Methyl *o*-Alkynylbenzoate[a]



[a]Reaction conditions: **1** (1.0 mmol) and $PhICl_2$ (1.2 mmol) in solvent (8 mL) for 15 min, isolated yield from chromatography/crystallization (yields in parentheses). [b]Using 2.0 equiv of $PhICl_2$, 1.5 h.

To our surprise, substrates bearing a MeO R^1 substituent at different positions of the aromatic ring gave different results (Scheme 3). Substrate **1u** with a MeO group at the *para*

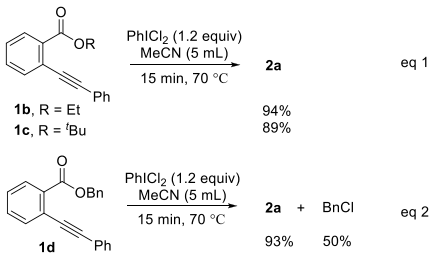
Scheme 3. Halocyclization of Methyl *o*-Alkynylbenzoate Bearing an OMe Substituent at Different Positions



position of the methoxyl carbonyl substituent underwent the halocyclization process smoothly, affording the desired product **2u** in an 83% yield. However, substrate **1v** with the MeO substituent at the *para* position of the alkyne moiety reacted to afford a mixture of the *trans*- and *cis*-dichloronated alkenes, with no desired cyclized product formed at all.

To further investigate the halocyclization process, ethyl, benzyl, and *tert*-butyl *o*-alkynylbenzoates were prepared and subjected to the standard conditions. As expected, substrates **1b–d** were compatible with the method, offering the desired product **2a** in 94%, 89%, and 93% yields, respectively (Scheme 4a,b). It is noteworthy that for the reaction of substrates **1d**, the formation of BnCl could be detected, which provided evidence for the mechanistic pathway of this transformation.

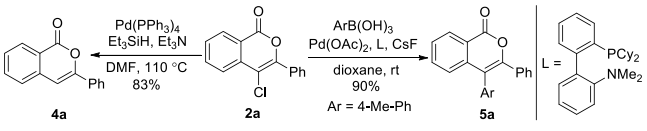
Scheme 4. Further Investigation of the Halocyclization of Ethyl, Benzyl, and *tert*-Butyl *o*-Alkynylbenzoates



Because of the mild reaction conditions and convenience of the procedure, we performed a scale-up experiment on substrate **1a**. It was found that the reaction of 2 g of substrate **1a** afforded 1.63 g of **2a** in 75% yield, indicating that a large-scale synthesis of 4-chloroisocoumarin is practical using this metal-free method. In addition, when the reaction mixture was cooled, a simple filtration was sufficient to isolate **1a** in the form of needles, obviating the need for purification by silica gel column chromatography.

One application of the 4-chloroisocoumarins obtained is to convert them to other building blocks by known methods. For example, reductive dechlorination of 4-chloroisocoumarin **2a** under conditions of $Pd(PPh_3)_4$, Et_3SiH, and Et_3N in DMF[51,52] led to formation of the corresponding 4-unsubstituted isocoumarin **4a** in good yield. Furthermore, Suzuki–Miyaura coupling of **2a** with 4-methylbenzeneboronic acid in the presence of a L/Pd catalyst system and CsF[53] furnished 4-arylisocoumarin **5a** in 90% yield (Scheme 5).

Scheme 5. Further Derivatization of 4-Chloroisocoumarin 2a



A literature survey indicated that the $PhICl_2$-mediated reactions could use either a radical or an ionic pathway.[47] In this regard, we conducted a series of control experiments to gain further insight into the reaction mechanism of this transformation. When the radical scavengers, including TEMPO, *tert*-butylhydroxytoluene (BHT), and 1,1-diphenylethene, were introduced into the reaction mixture of substrate **1a**, almost no desired product **2a** was obtained in any case. However, considering that $PhICl_2$ could be consumed by the radical scavenger[47,54,55] and then the reaction could be disabled, we postulated that an ionic pathway cannot be completely ruled out. Our control experiment showed that when methanol was used as the solvent for substrate **1a**, the reaction could not afford the desired product **2a** at all. This result might support an ionic mechanism for this reaction, as a radical pathway generally should not be affected by the use of a protic polar solvent. On the other hand, a radical-based mechanism could be supported by a radical clock experiment in which a cyclopropane-derived substrate would deliver a ring-

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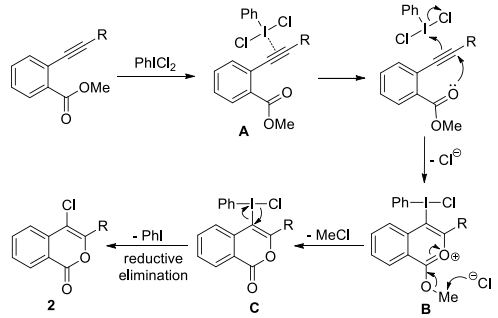
open product.[56,57] However, for the reaction of substrate **1r** with a cyclopropyl substituent, we found that no ring-open product could be observed.

On the basis of these results, we tentatively proposed an ionic pathway for this reaction.[37,58] First, the alkyne triple bond coordinates with $PhICl_2$ to give intermediate **A**. Next, a concerted process involving the nucleophilc attack of the carbonyl oxygen atom of the ester group on the triple bond and the triple bond on the iodine center to $PhICl_2$ occurs affording the oxonium ion intermediate **B**, with the formation of a C−I bond and release of a chloride anion. Next, chloride nucleophilically attacks the methyl carbon center in **B**, leading to the formation of intermediate **C**. While in the case of *tert*-butyl ester **1d**, the removal of the *tert*-butyl group should occur by an S_N1 mechanistic pathway. Finally, reductive elimination of PhI in **C** affords the title product (Scheme 6). We

Scheme 6. Proposed Pathway for the Halocyclization of Methyl *o*-Alkynylbenzoates

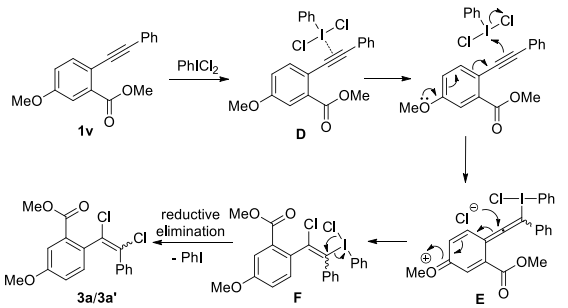


tentatively proposed that the failure of substrate **1t** might be attributed to unstable intermediate **B** with an *n*-butyl R group, which might easily undergo a *β*-H elimination to give some unstable allene byproduct.

The alternative outcome of the reaction of substrate **1v** might also support an ionic pathway: because of the presence of the MeO substituent at the *para* position of the alkyne moiety in substrate **1v**, the reaction of **1v** with $PhICl_2$ gives an allene intermediate **E**. Then the nucleophilic attack of the chloride anion on the quaternary center of allene gives intermediate **F**. Finally, the reductive elimination of PhI in **F** affords the title product (Scheme 7).

In conclusion, we have developed a novel and efficient approach to constructing the 4-chloroisocoumarin skeleton through halocyclization of *o*-alkynylbenzoate derivatives using $PhICl_2$ as both the oxidant and the chlorine source. This hypervalent iodine-mediated oxidative cyclization approach, which involves both C−Cl and C−O bond formation, has the advantages of mild reaction conditions, simple operation, fast, easy purification, large-scale preparation, and metal-free features. Further investigation of the reaction mechanism is still ongoing in our lab.

Scheme 7. Proposed Alternative Pathway for the Reaction of 1v



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00047.

Experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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