Ag$_2$O-mediated Tandem Reaction between Terminal Alkyne and o-Iodibenzoic Acid: Construction of 3-Ethylideneisobenzofuran-1(3H)-ones

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ABSTRACT: Taking aryl propargyl ether and o-iodibenzoic acid as substrates, a series of aryl cyclolactones bearing an exocyclized C–C bond were constructed with moderate to good yields. Diverse substituent groups could be tolerant in the reaction, which indicated excellent compatibility of the reaction. In this tandem reaction, Ag$_2$O was employed as the media and Et$_3$N was screened as the base to facilitate the reaction. A concise mechanism was proposed on the basis of the expansion of the substrates and theoretical analysis. Sonogashira type coupling coupled with intramolecular nucleophilic addition in one pot to construct the product, 3-ethyldeneisobenzofuran-1(3H)-one.

1. INTRODUCTION

Both terminal alkyne and o-iodibenzoic acid are valuable chemical motifs used in organic synthesis. With the electron deficiency and coordination of unsaturated carbon–carbon triple bonds, terminal alkyne was widely used in organic synthesis. In addition to the presence in natural products, terminal alkynes were also used to construct macrocycles as well as other practical chemicals.1 Benefiting from the structural superiority, it was convenient for terminal alkyne to be employed in diverse reactions.2 Particularly, alkyne was a conventional scaffold employed in click chemistry to construct azoles.3 Also, terminal alkyne could act as a module to participate in intramolecular/intermolecular cyclization.4 Moreover, in reactions of metathesis as well as coupling reactions, alkyne were used as pattern substrates.5 As documented, upon coordinating to metal catalysis, alkyne could form metal acetylene intermediates to be more susceptible.6 In this way, sonogashira coupling would take place between terminal alkyne and halide.7 Similarly, in the presence of a transition metal catalyst, terminal alkyne could participate in the Castro–Stephens coupling, Eglinton coupling, Glaser–Hay coupling, and so on.8 Coincidentally, another facile scaffold, o-iodobenzoic acid, was often employed to prepare hypervalent iodine reagents.9 Conveniently, o-iodobenzoic acid could be oxidized to 2-iodoxybenzoic acid (IBX), which were excellent oxidants.10 With the presence of iodine in the skeleton, o-iodobenzoic acid could participate into metal-catalyzed coupling reactions. Reacting with carbodiimides, Duangjan and co-workers prepared a series of quinazolininediones taking o-iodobenzoic acid as the substrate.11 Furthermore, chelating with metal catalysis, o-iodobenzoic acid could act as a self-contained directing-group substrate.12 Based on the advantage of both sides, it would be desired to witness the reaction between terminal alkyne and o-iodobenzoic acid. In 2018, Mancuso et al.13 disclosed the Cu-catalyzed cycloisomerization of 2-alkynylbenzoic acid and Chaudhary et al.14 reported the Ag$_2$O nanoparticle-catalyzed 5-exo-dig cyclization between o-iodobenzoic acid and phenylacetylene. Even so, subjected to either the complexity of substrate or the expensiveness of the catalyst, reactions referred above had not been properly applied. Herein, under alkaline conditions, an Ag(I)-mediated coupling sequentially followed by intramolecular cyclization would be disclosed. A series of aryl cyclolactone bearing an exocyclized C–C bond were obtained through the expansion of terminal alkyne as well as o-iodobenzoic acids.

2. RESULT AND DISCUSSION

Aryl propargyl ether, derived from phenol and propargyl bromide, together with o-iodobenzoic acid was selected as the substrate to conduct the optimization of the reaction. Initially, idiomatic conditions for the Cu(I)-catalyzed Ullmann-type coupling reaction were employed to conduct the reaction. Taking cuprous iodide (CuI) coordinated with 1,10-phenanthroline (o-phen) as the catalyst, potassium acetate (KOAc) to be the base, and silver trifluoromethanesulfonate (AgOTf) as the oxidant, the reaction was conducted in the solvent of toluene under the protection of N$_2$. To our delight, an aryl cyclic lactone bearing an exocyclized C–C bond product, compound 3, was obtained with the yield of 56%. Then, we...
move forward to the optimization of the condition (listed in Table 1). Regrettably, no target product could be detected without the presence of AgOTf. When it turns to the absence of CuI/o-phen., the reaction was not affected and the target product was obtained with a 53% yield as scheduled. These results indicate that the tendentious Ullmann-type coupling reaction did not take place. Unceasingly, reducing the dosage of KOAc to 1.0 eq would also prevent the reaction from happening. Whereas, decreasing the dosage of the oxidant, AgOTf, to 0.1 eq would remarkably lower the production of to 12% yield. Based on these, the dosage of AgOTf and KOAc was still maintained at 1.0 and 2.0 equiv respectively.

Table 1. Optimization of the Reaction

| entry | conditions | yield |
|-------|------------|-------|
| 1     | CuI 5%, o-phen 5%, KOAc 2.0 eq, AgOTf 1.0 eq, toluene, N2, 100 °C | 56%   |
| 2     | CuI 5%, o-phen 5%, KOAc 2.0 eq, toluene, N2, 100 °C | 0     |
| 3     | KOAc 2.0 eq, AgOTf 1.0 eq, toluene, N2, 100 °C | 53%   |
| 4     | KOAc 1.0 eq, AgOTf 1.0 eq, toluene, N2, 100 °C | 0     |
| 5     | KOAc 2.0 eq, AgOTf 0.1 eq, toluene, N2, 100 °C | 12%   |
| 6     | KOAc 2.0 eq, AgOTf 1.0 eq, toluene, N2, 100 °C | 36%   |
| 7     | KOAc 1.0 eq, AgOTf 0.1 eq, toluene, N2, 100 °C | 0     |
| 8     | KOAc 2.0 eq, AgOTf 1.0 eq, toluene, N2, 100 °C | 52%   |
| 9     | KOAc 2.0 eq, AgOTf 1.0 eq, toluene, N2, 100 °C | 43%   |
| 10    | KOAc 2.0 eq, AgOTf 1.0 eq, toluene, N2, 100 °C | 43%   |
| 11    | KOAc 2.0 eq, AgOTf 1.0 eq, toluene, N2, 100 °C | 64%   |
| 12    | KOAc 2.0 eq, AgOTf 1.0 eq, toluene, N2, 100 °C | 81%   |
| 13    | KOAc 2.0 eq, AgOTf 1.0 eq, toluene, N2, 100 °C | 82%   |
| 14    | KOAc 2.0 eq, AgOTf 1.0 eq, toluene, N2, 100 °C | 82%   |
| 15    | KOAc 2.0 eq, AgOTf 1.0 eq, toluene, N2, 100 °C | 82%   |
| 16    | KOAc 2.0 eq, AgOTf 1.0 eq, toluene, N2, 100 °C | 78%   |

Table 2. Expansion of Terminal Alkynes

![Table 2](https://doi.org/10.1021/acsomega.1c06177)

methoxy group at different positions, an electron-donating group, were compared. Also, a para-methoxyl product, 3ca, was obtained with the highest yield of 92%. Relatively, aryl propargyl ether with the methoxyl located at the meta-site, substrate 1g, yielded the lowest product with 87%, which may due to the weaker electron-donating capacity to the meta-site (product 3ga, Table 2).

On the other hand, the diversity of substituents at the side of o-iodibenzoic acid were screened immediately. As shown, halogens, which usually seemed as the ortho and para directing group, were selected to conclude the electronic effect. Generally, for the electron-withdrawing property, halogen-substituted o-iodibenzoic acids were less active (comparing the yields of 3aa, 3ab, 3af, and 3aj, Tables 2 and 3). From the yield of relevant products, it could be noted that relatively minimal inhibition of the reaction was shown by bromine when located at the same position on o-iodibenzoic acid (comparing the yield of 3ab with 3af and 3aj, 3ac with 3ag and 3ak, and 3ad with 3ah and 3al, Table 3). Theoretically, bromine in different positions showed multifarious effects on the reaction. Thereinto, with comparison of the yields of 3ab, 3ac, 3ad, and 3ae, the highest yield was obtained when bromine was at the para-position of iodine. Comparatively, it would be more imperative to the reaction when bromine is located at the ortho- and para-positions of iodine other than carboxyl (compared the yields of 3ab to 3ae and 3ac to 3ad, Table 3). The deep cause is the presence of an electron-withdrawn group that would be positive to the stability of carboxylic acid anions formed during the reaction. Similarly, when the more electron-withdrawing
transiently. Under the alkaline environment created by Et₃N, aromatic carboxylic acid, intermediate 4 was formed transiently. Under the alkaline environment created by Et₃N, the carboxyl group dissociated out of H⁺ quickly. Intramolecularly, the carboxylate group attracted the electron deficient alkyne group and nucleophilic addition was achieved. Ultimately, the aryl cyclo lactone bearing an exocyclized C=C bond, compound 3, was generated. There is, in addition, one further point to make. Taking the distinct expression of different substituted groups on both substrates into consideration, it could be concluded that the electronic effect of the substituted groups on the side of aryl propargyl ether dominated the formation of intermediate 4. When it turns to the intramolecular nucleophilic addition, the electronic effect of the substituent groups on the side of o-iodibenzoic acid would be more decisive.

3. CONCLUSIONS
In a word, a tandem reaction between aryl propargyl ether and o-iodibenzoic acid was documented. After indispensable optimization of the reaction condition, 28 examples of aryl cyclolactone bearing an exocyclized C=C bond were constructed through the Ag(I)-mediated coupling, sequentially followed by intramolecular cyclization. Excellent compatibility with substituent groups such as the aldehyde group was demonstrated. Based on the screening of the substrate structure, divergent affections on the reaction stood out. Taking electronic effects into account, the underlying mechanism was proposed.

4. EXPERIMENTAL SECTION
To an oven-dried Schlenk tube charged with nitrogen (N₂), propargyl ether (substrate 1, 0.5 mmol), o-iodibenzoic acid (0.5 mmol), and Ag₂O (1.0 eq) were added. Being evacuated and back-filled with N₂ for three times, triethylamine (Et₃N, 1.0 mmol, 2.0 eq) was injected. Then, the mixture was left standing overnight. After stirring for 24 h at 100 °C, TLC analysis (PE/EtOAc, v/v = 20:1) was performed on the detection of the reaction, which showed the complete consumption of substrates. After quenching, 20 mL EtOAc was added to the reaction solution. Directly, the mixture was passed through silica gel column and rinsed with additional 30 mL EtOAc. The filtrate was combined and concentrated on a rotary evaporator. Further purification was conducted through column chromatography (PE/EtOAc, v/v = 30/1–40/1). If necessary, recrystallization from EtOAc could provide the target product as white crystalline powder.

ASSOCIATED CONTENT
Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c06177.

Experiment, characterization data, and NMR spectra (PDF)

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Author Contributions
H.-F.H. proposed the idea and carried out the primary part of the experiment. Y.W., C.Z., and Z.T. carried out part of the isolation and purification of the compounds. Y.X. and J.Y. participated in the revision of the manuscript.
Notes
The authors declare no competing financial interest.

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