Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Regioselective Neighboring-Group-Participated 2,4-Dibromohydration of Conjugated Enynes: Synthesis of 2-(2,4-Dibromobut-2-enoyl)benzoate and Its Applications

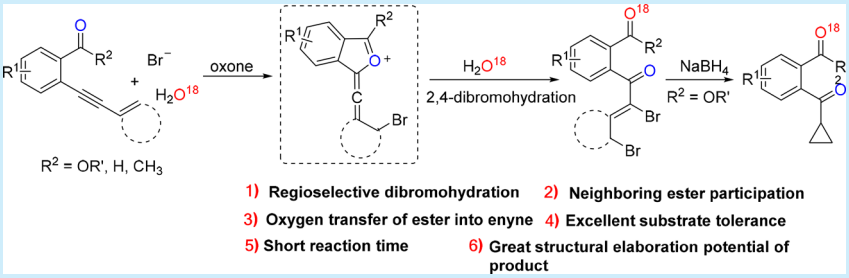
Si-Tian Yuan,[†,‡] Hongwei Zhou,[†] Liang Gao,[§] Jin-Biao Liu,[*,‡] and Guanyinsheng Qiu[*,†]

[†]College of Biological, Chemical Science and Engineerindg, Jiaxing University, 118 Jiahang Road, Jiaxing 314001, China

[‡]School of Metallurgical and Chemical Engineering, Jiangxi University of Science and Technology, 86 Hongqi Road, Ganzhou 341000, China

[§]Department of natural Science and Computer Science, Ganzhou Teacher's College, Ganzhou, 341000, China

Supporting Information



ABSTRACT: A regioselective 2,4-dibromohydration of conjugated enynes is reported for the synthesis of 2-(2,4-dibromobut-2-enoyl)benzoate. In the presence of tetra-*n*-butylammonium bromide and H_2O the transformation proceeds smoothly with good reaction efficiency and a broad reaction scope. Mechanism studies indicate that the neighboring ester group participates in the 2,4-dibromohydration, and the oxygen atom of ester is transferred into the C−C triple bond to form the keto carbonyl group in the product. 2-(2,4-Dibromobut-2-enoyl)benzoate is recognized as an important synthon toward phthalazin-1(2*H*)-one and the natural product *Shihunine*.

Alkyne-based chemistry has attracted continuous interest from chemists due to its versatility in structural elaboration for the synthesis of diverse architectures.[1] To date, it was generally accepted that regioselectivity was still challenging for some internal alkyne-based transformations. Consequently, many research groups devoted themselves to developing new strategies to control reaction regioselectivity.

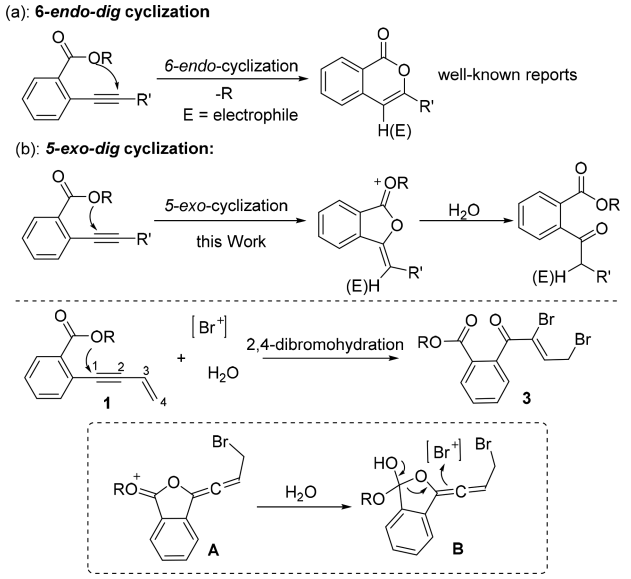
o-Alkynylbenzoate was a powerful dual-function building block.[2−6] It was impressive that cyclization of *o*-alkynylbenzoate was highly regioselective in a 6-*endo-dig* fashion, leading to an isocoumarin core. A Brønsted acid,[3] Lewis acid,[4] and transitional metal[5] could enable this 6-*endo-dig* cyclization. The same regioselectivity was observed to offer 4-substituted isocoumarins through an electrophilic 6-*endo-dig* cyclization when *o*-alkynylbenzoate was treated with an electrophile (such as Br_2, I_2, ICl, disulfane, etc.).[6] Considering our continuous interests in developing application of dual-functional substrates in organic synthesis,[7] we were focused mainly on *o*-alkynylbenzoate chemistry with a wish to exploit diverse *o*-alkynylbenzoate-based transformations. Accordingly, a *N*-bromosuccinimide (NBS)/water-mediated diketonization of *o*-alkynylbenzoate was established by our group for the synthesis of benzil-*o*-carboxylates.[8] Interestingly, the diketonization of *o*-alkynylbenzoate was ascribed to a neighboring-ester-participated 1,1-dibromohydration of alkyne. Combined with the well-recognized electrophilic 6-*endo-dig* bromocyclization of *o*-alkynylbenzoate, the 1,1-dibromohydration was finally accomplished by an NBS-assisted nucleophilic ring opening, thus presenting an oxygen atom transfer of ester into the C−C triple bond. Mechanism studies suggested that an occurrence of water probably changed the reaction pathway. To the best of our knowledge, it was surprising to find that the annulation type of 6-*endo-dig* dominated 2-alkynylbenzoate-based cyclization. On the other hand, 5-*exo-dig* cyclization always required the use of 2-alkynylbenzoic acid as the substrate or the assistance of transitional metal catalysis and a base.[9] Inspired by the above information, we disclosed an electrophilic 5-*exo-dig* cyclization of 2-alkynylbenzoate (Scheme 1b). In the process, we envisioned that the intermediate isobenzofuran-1(3*H*)-one cation formed herein did not go through removal of the substituent R, but underwent an oxygen transfer reaction toward useful building blocks (Scheme 1b).

As we know, an electrophilic bromination of enyne is preferred to occur on the double bond.[10] Combined with 5-*exo-dig* cyclization, an electrophilic bromocyclization of *o*-enynylbenzoate **1** thus provided an intermediate **A**. Treated with water, the

Received: November 26, 2017

DOI: 10.1021/acs.orglett.7b03671
Org. Lett. XXXX, XXX, XXX−XXX

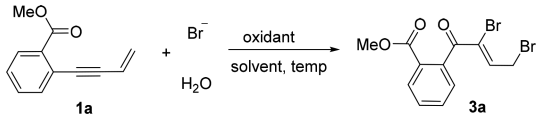
Scheme 1. Neighboring-Ester-Participated 2,4-Dibromohydration of Enynes



intermediate **A** underwent a nucleophilic addition, resulting in an intermediate **B**. Finally, an electrophile-assisted ring opening happened to the intermediate **B** to give 2,4-dibromohydrative product **3**. Based on the above proposed pathway, it was reasonable that an oxygen atom of ester group was transferred into the C−C triple bond to form a keto carbonyl group, and dibromo atoms were regioselectively installed into the C2 and C4 position of enyne function, respectively. Interestingly, a formal 5-*exo* annulation of the alkynyl group in *o*-enynylbenzoate **1** was observed in the reaction. Distinctively, an elegant example reported by Larock indicated that the electrophilic halocyclization of *o*-enynylbenzoate **1** took place on the C−C triple bond to provide isocoumarin derivatives.[11] This discrepancy implied that the reaction developed herein represented a novel supplement of 2-enynylbenzoate-based transformations. To verify the practicality of the projected transformation, we started to optimize the reaction.

Initially, methyl *o*-enynylbenzoate **1a** was employed as a model substrate. For convenience, we directly used a mixed solvent containing water as a source of the substrate water. A preliminary result from screening electrophilic bromo sources showed that the use of NBS enabled 2,4-dibromohydration of **1a**, leading to a desired product **3a** in 13% yield (entry 1, Table 1). This promising result encouraged us to investigate more impactful factors. Considering our findings on bromide-mediated oxidative bromination,[8,12] we geared the bromo source to tetra-*n*-butylammonium bromide (TBAB). Accordingly, various oxidants were evaluated (entries 2−6, Table 1). From the screening results, it seemed that oxone was the best choice,[13] providing the desired product **3a** in 70% yield (entry 6, Table 1), and the model reaction completed within 0.5 h. Other oxidants including $Cu(OAc)_2$, TBHP, $K_2S_2O_8$, and $(NH_4)_2S_2O_8$ did not give better yields. Optimization on various bromide sources implied that the use of KBr and $ZnBr_2$ did not improve reaction efficiency (entries 7−8, Table 1). It was probably attributed to the fact that TBAB behaved as a phase transfer catalyst, thus enhancing the reaction. Subsequently, the solvent effect was also checked. Inferior yields were observed when mixed solvents including THF/H_2O and MeCN/H_2O were employed (entries 9−10, Table 1). Since 2 mol of bromo atom were incorporated into the product **3a**, an excess of bromo sources (mol ratio Br^-/**1a** = 3/1) was surveyed. As expected, the yield of **3a** was improved to 78% when 3.0 equiv of TBAB were used (entry 11, Table 1). A further increase of TBAB loading did not make a significant impact on the yield of **3a** (entry 12, Table 1). After screening the percentage of water in the mixed solvent, it was found that DCE/H_2O (1:1, v/v) was the best solvent system. An increase in the reaction temperature was not favorable for the reaction (entry 15, Table 1). Thus, we determined the optimized conditions as follows: 3.0 equiv of TBAB, 2.0 equiv of oxone, DCE/H_2O (2.0 mL, v/v = 1:1) at room temperature.

Table 1. Three-Component Synthesis of 3a: Survey of Reaction Conditions[a]



entry	Br source	oxidant	solvent	yield (%)[b]
1	NBS	–	DCE/H_2O (1:1, v/v)	13
2	TBAB	TBHP	DCE/H_2O (1:1, v/v)	trace
3	TBAB	$Cu(OAc)_2$	DCE/H_2O (1:1, v/v)	complex
4	TBAB	$K_2S_2O_8$	DCE/H_2O (1:1, v/v)	20
5	TBAB	$(NH_4)_2S_2O_8$	DCE/H_2O (1:1, v/v)	35
6	TBAB	oxone	DCE/H_2O (1:1, v/v)	70
7	KBr	oxone	DCE/H_2O (1:1, v/v)	53
8	$ZnBr_2$	oxone	DCE/H_2O (1:1, v/v)	27
9	TBAB	oxone	THF/H_2O (1:1, v/v)	64
10	TBAB	oxone	MeCN/H_2O (1:1, v/v)	65
11[c]	**TBAB**	**oxone**	**DCE/H_2O (1:1, v/v)**	**78**
12[d]	TBAB	oxone	DCE/H_2O (1:1, v/v)	75
13[c]	TBAB	oxone	DCE/H_2O (4:1, v/v)	56
14[c]	TBAB	oxone	DCE/H_2O (1:4, v/v)	49
15[c,e]	TBAB	oxone	DCE/H_2O (1:4, v/v)	48

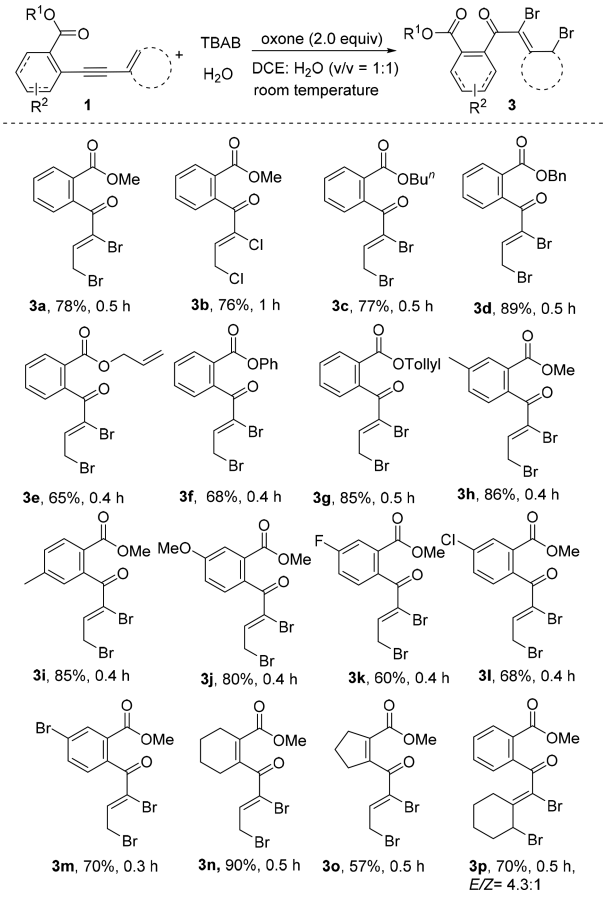
[a]Standard conditions: enyne **1a** (0.2 mmol), bromo source (0.5 mmol), oxidant (0.4 mmol), solvent (2.0 mL), rt. [b]Isolated yield based on enyne **1a**. [c]TBAB (0.6 mmol). [d]TBAB (0.8 mmol). [e]The reaction was run at 50 °C. NBS = *N*-bromosuccinimide; TBAB = *tetra-n*-butylammonium bromide; TBHP = *tert*-butyl hydroperoxide; oxone = potassium peroxylmonosulfate ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$).

With the optimized conditions in hand, we then explored the reaction scope and generality. The results are illustrated in Scheme 2. From the results, we were pleased to find that a series of 2,4-dibromohydrative products **3** were achieved in good yields. Interestingly, 2,4-dichlorohydration was observed when *tetra-n*-butylammonium chloride (TBAC) replaced TBAB under standard conditions, leading to a desired product **3b** in 76% yield. Various *o*-enynylbenzoates were compatible, and the corresponding products **3c**−**3g** were provided in 65−89% yields. For example, allylic benzoate **1e** was a good reaction partner, resulting in **3e** in a moderate yield. The reaction of tollyl benzoate **1g** gave rise to **3g** in 85% yield. The structure of the product **3g** was verified by X-ray diffraction (CCDC number: 1572355). According to the structure of **3g**, we determined the exact structures of other products.

The substituent effect of R^2 was explored as well. Based on the results, it was found that the substrates with methyl, methoxyl, fluoro, chloro, and bromo at the R^2 position of the phenyl ring were compatible for the reaction under standard conditions. Interestingly, the reaction of cyclohexene-connected enyne ester **1n** delivered a corresponding product **3n** in an excellent yield (90%). To our surprise, the reaction efficiency was greatly

DOI: 10.1021/acs.orglett.7b03671
Org. Lett. XXXX, XXX, XXX−XXX

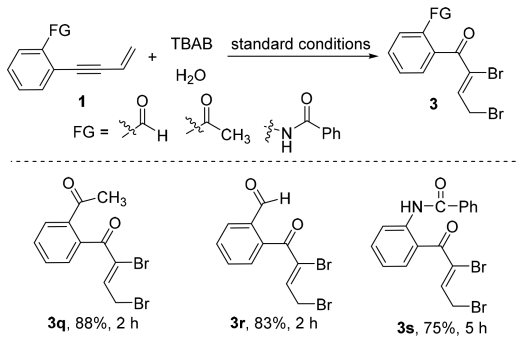
Scheme 2. Synthesis of 2-(2,4-Dibromobut-2-enoyl)benzoate



hindered when a cyclopentene-linked substrate **1o** was used. A corresponding product **3o** was obtained in 57% yield. The reaction of methyl 2-(cyclohex-1-en-1-ylethynyl)benzoate **1p** was also tested. Desired product **3p** was observed in 70% yield accordingly. Based on NMR data analysis, we found that **3p** was a mixture of two *E*/*Z* isomers, and the ratio was 4.3:1. To our surprise, other substituted enyenes such as 2-(pent-3-en-1-yn-1-yl)benzoate and 2-(3-phenylbut-3-en-1-yn-1-yl)benzoate were not tolerated accordingly.

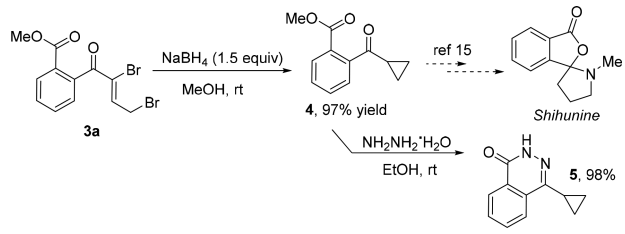
Subsequently, we investigated other neighboring groups. As presented in Scheme 3, the neighboring groups could be the aceto group, aldehyde group, and benzamide group. The dibromohydration worked well under standard conditions, and the corresponding products **3q**−**3s** were prepared in 75−88% yields.

Scheme 3. Effect of Various Neighboring Groups



To exploit applications of the products **3** in organic synthesis, a reduction of a keto group of the product **3a** was carried out in the presence of $NaBH_4$/MeOH at room temperature (Scheme 4).

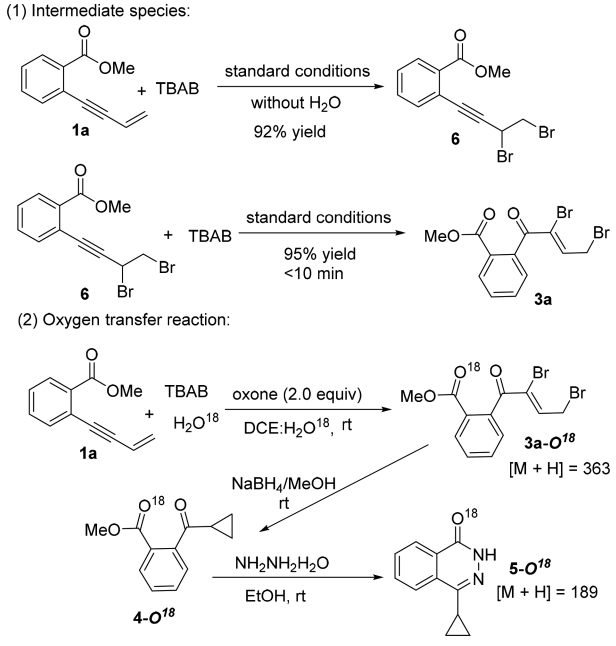
Scheme 4. Application Exploration of the Product 3a



Surprisingly, the keto carbonyl group in product **3a** survived in the reaction, and a distinctive compound **4** was synthesized in 97% yield through a debrominative cyclopropanation. To the best of our knowledge, **4** was an important synthon toward a privileged structural core phthalazin-1(2*H*)-one **5**. Moreover, **4** was also a key intermediate for a total synthesis of natural product *Shihunine*.[14]

On the basis of the aforementioned results, several control experiments were conducted. As shown in Scheme 5, the reaction

Scheme 5. Control Experiments



of **1a** in the absence of water was first run. A dibrominative product **6** was uniquely observed in 92% yield. The formation of compound **6** was attributed to an electrophilic 1,2-dibromination of enyne function. Interestingly, under standard conditions the compound **6** converted into the 2,4-dibromohydrative product **3a** in 95% yield within 10 min.[15] However, we did not detect the formation of **6** when **1a** was treated with TBAB under standard conditions.

To identify the oxygen atom transfer reaction illustrated in Scheme 1, we started the reaction of **1a** at DCE/H_2O^{18} (Scheme 5). Electrospray ionization mass spectroscopic analysis of the product **3a**-O^{18} showed a strong signal at [M + H] = 363, suggesting 1 equiv of H_2O^{18} was incorporated into **3a**. To clarify the exact site of oxygen-18, the reduction and condensation of

DOI: 10.1021/acs.orglett.7b03671
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3a-O^{18} with hydrazine were conducted. The reaction offered the desired phthalazin-1(2*H*)-one **5-**O^{18}. Electrospray ionization mass spectroscopic analysis showed the product **5-**O^{18} contained one oxygen-18, whose [M + H] was equal to 189. The above information implied that 1 equiv of water was installed into the ester group, and the oxygen atom of ester was transferred into the C−C triple bond to form a keto carbonyl group.

In conclusion, we have developed a regioselective neighboring group-participated 2,4-dibromohydration of *o*-enynylbenzoate for the synthesis of 2-(2,4-dibromobut-2-enoyl)benzoates in good to excellent yields. The transformation worked well in the presence of TBAB and oxone at room temperature. Mechanism studies showed that an oxygen atom transfer of ester was involved. The detailed mechanism and application of the product in organic synthesis are ongoing in our group, and the results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03671.

Experimental procedures, product characterization data, ^{1}H and ^{13}C NMR spectra for new compounds (PDF)

Accession Codes

CCDC 1572355 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: qiuguanyinsheng@mail.zjxu.edu.cn (G.Q.).
*E-mail: liujbgood@hotmail.com (J.L.).

ORCID

Hongwei Zhou: 0000-0001-8308-960X
Guanyinsheng Qiu: 0000-0002-6587-8522

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the Natural Science Foundation of China (Nos. 21502069, 21502075, 21762018, and 21772067), the Natural Science Foundation of Jiangxi Province (20171BAB213008), the Postdoctoral Science Foundation of Jiangxi Province (2017KY22), and Science and Technology Project of Jiangxi Provincial Education Department (No. 151357) is gratefully acknowledged.

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DOI: 10.1021/acs.orglett.7b03671
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