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Metal-Free Oxidative Radical Alkynylation/Ring Expansion Rearrangement of Alkenyl Cyclobutanols with Ethynylbenziodoxolones

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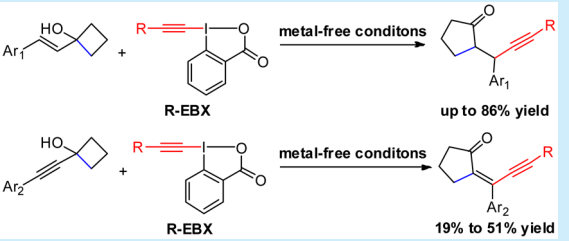
Supporting Information

ABSTRACT: The first metal-free alkynylation/ring expansion cascade process of alkenyl cyclobutanols with ethynylbenziodoxolones has been developed. A variety of synthetically valuable β-alkynylated cyclopentanones were prepared in moderate to good yields. Alkynyl cyclobutanols could also undergo this transformation, providing a new approach to substituted ene-yne-carbonyl compounds.



Substituted cyclopentanones are valuable scaffolds, as they widely exist in medicinal molecules[1] and are utilized as intermediates for natural product syntheses.[2] Much more attention has been focused on the development of synthetic methodologies in this area. Among this research, ring expansion rearrangement reactions of vinylcyclobutanol derivatives have been recognized as one of the most powerful methods for synthetically useful substituted five-membered ring systems.[3] Alexakis's group realized enantioselective fluorination and iodination/ring expansion reaction of strained allylic alcohols to synthesize a series of β-halofunctionalization spiroketones (Scheme 1a).[4] Later, You et al. reported the synthesis of 2-alkyl-2-aryl cycloalkanones by a highly enantioselective chlorination/ring expansion cascade (Scheme 1a).[5] Recently, Glorius et al. expanded the reaction to trifluoromethylation under visible-light-mediated photo-redox-catalyzed conditions (Scheme 1b).[6] Additionally, arylation and alkylation could also be successfully applied to the cascade process reported by the groups of Toste[7] and Tu[8] (Scheme 1c). On the other hand, good work on the ring opening/alkynylation of cycloalkanols was realized previously (Scheme 1d).[9] In spite of the notable advances, there is still no efficient approach for the one-step alkynylation and ring expansion rearrangement of vinylcyclobutanol. Alkynes are not only important structural motifs in a broad range of natural products, bioactive compounds, and materials but also valuable building blocks in organic synthesis due to their versatile transformations.[10] Thus, the investigation toward tandem alkynylation/ring expansion rearrangement is highly desirable.

Ethynylbenziodoxolone (EBX) as one of the most powerful and useful alkynylating reagents has been increasingly investigated over the past few years because of its stability toward air and moisture. Since 2009, EBX has been applied for the direct C−H alkynylation of a range of (hetero)aromatic rings with the use of transition metal catalysts.[11,12] Furthermore, EBX reagents are also ideally suited for the alkynylation of carbon nucleophiles[13] and radicals[14] under metal-free conditions, making alkynylation much more convenient and environmentally friendly. Encouraged by our previous work[14c,d] and recent progress in ring rearrangement radical reactions,[6] we envisioned that EBX might be applied to ring rearrangement to afford useful alkynylated five-membered ring derivatives. Herein,

Scheme 1. Recent Developments on Ring Expansion Rearrangement of Vinylcyclobutanol and Ring-Opening Alkynylation of Cycloalkanols

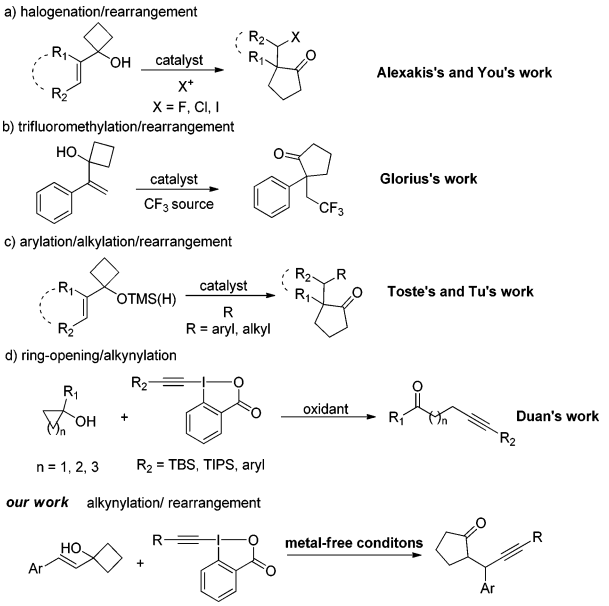


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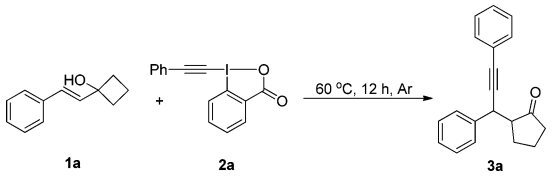
Table 1. Optimization of Reaction Conditions[a]



entry	**1a**/**2a** (equiv)	catalyst (20%)	oxidant (equiv)	solvent (1 mL/1 mL)	yield[b] (%) (dr)
1	3:1	$AgBF_4$	$K_2S_2O_8$ (2.0)	$MeCN/H_2O$	68 (2.2:1)
2	3:1	Bu_4NI	$K_2S_2O_8$ (2.0)	$MeCN/H_2O$	49 (2.8:1)
3	3:1	KI	$K_2S_2O_8$ (2.0)	$MeCN/H_2O$	41 (2.4:1)
4	3:1		$K_2S_2O_8$ (2.0)	$MeCN/H_2O$	69 (1.9:1)
5	2:1		$K_2S_2O_8$ (2.0)	$MeCN/H_2O$	65 (1.7:1)
6	1:2		$K_2S_2O_8$ (2.0)	$MeCN/H_2O$	trace
7	3:1		$K_2S_2O_8$ (3.0)	$MeCN/H_2O$	68 (1.6:1)
8	3:1		$K_2S_2O_8$ (4.0)	$MeCN/H_2O$	76 (1.6:1)
9	3:1		$K_2S_2O_8$ (5.0)	$MeCN/H_2O$	67 (1.9:1)
10	2:1		$K_2S_2O_8$ (4.0)	$MeCN/H_2O$	57 (1.6:1)
11	3:1		$Na_2S_2O_8$ (4.0)	$MeCN/H_2O$	71 (1.7:1)
12	3:1		$(NH_4)_2S_2O_8$ (4.0)	$MeCN/H_2O$	6
13	3:1		TBHP (4.0)	$MeCN/H_2O$	15
14	3:1		*m*-CPBA (4.0)	$MeCN/H_2O$	nd
15	3:1		$K_2S_2O_8$ (4.0)	acetone/H_2O	67 (1.6:1)
16	3:1		$K_2S_2O_8$ (4.0)	toluene/H_2O	trace
17	3:1		$K_2S_2O_8$ (4.0)	DCE/H_2O	trace

[a]All reactions were carried out on a 0.2 mmol scale at 60 °C in 2 mL of solvent under an argon atmosphere for 12 h. [b]Yield of isolated product. Number in parentheses is dr values (determined by the yields of isolated isomers).

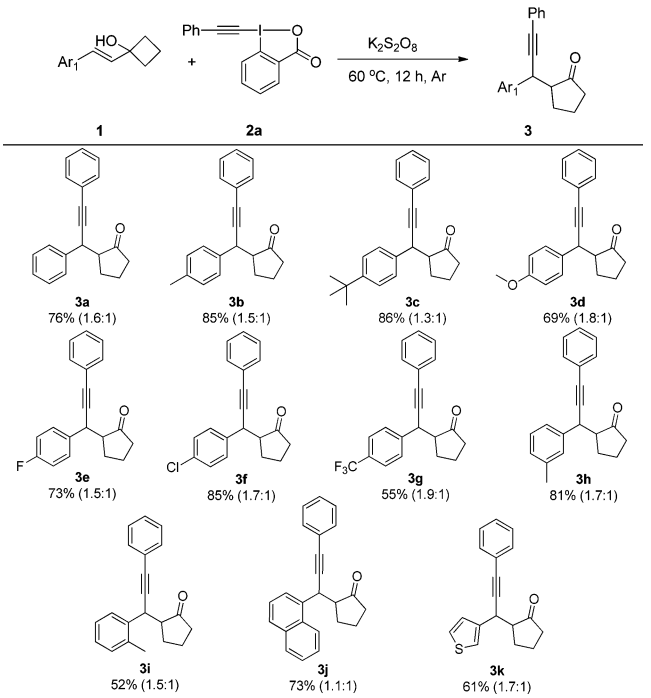
we describe the first metal-free oxidative radical alkynylation/ring expansion rearrangement of vinylcyclobutanol with the use of EBX.

Initially, we selected phenyl-1,2-benziodoxol-3(1*H*)-one (Ph-EBX) and (*E*)-1-styrylcyclobutanol as the standard substrates to optimize the reaction conditions (Table 1). With potassium persulfate ($K_2S_2O_8$) as the oxidant and silver tetrafluoroborate ($AgBF_4$) as the catalyst in aqueous media, CH_3CN/H_2O (1 mL/1 mL), at 60 °C, desired product **3a** was isolated in 68% yield (Table 1, entry 1). Then, to our delight, we found that the reaction proceeded smoothly in the absence of a catalyst (entry 4 vs entries 1−3), affording the desired product in a good yield of 69%. We further studied the effect of the amount of $K_2S_2O_8$ and **2a** on the reaction (entries 4−10), and the yield of the product further increased to 76% yield (entry 8). Subsequently, a few of other oxidants and solvents were also screened, but no further increase in the yield was observed (entry 8 vs entries 11−17).

The substrate scope was subsequently investigated under the optimized conditions. First, various substituted (*E*)-1-styrylcyclobutanols were applied to react with Ph-EBX. As shown in Scheme 2, several electron-withdrawing (**3e**−**3g**) and electron-donating (**3b**−**3d**) substituents on the benzene ring of (*E*)-1-styrylcyclobutanols were well-tolerated and furnished the corresponding products in moderate to good yields. The reaction was sensitive to steric hindrance. A significantly decreased yield was observed for the *ortho*-substituted alkenyl cycloalkanol in comparison with *para*- and *meta*-substituted substrates (**3i** vs **3b** and **3h**). Other aromatic substituted substrates were suitable for this transformation, as well, such as (*E*)-1-(2-(naphthalen-1-yl)vinyl)cyclobutanol (**3j**) and (*E*)-1-(2-(thiophen-3-yl)vinyl)cyclobutanol (**3k**).

We further evaluated the scope of the reaction by preparing several other EBX reagents with different substituents to react with (*E*)-1-styrylcyclobutanols under the developed conditions.

Scheme 2. Scope of Alkenyl Cyclobutanol 1[a]



[a]Reaction conditions: **2a** (0.2 mmol), **1** (3.0 equiv), $K_2S_2O_8$ (4.0 equiv), CH_3CN (1 mL)/H_2O (1 mL) under an argon atmosphere at 60 °C for 12 h. Yield of isolated product. Number in parentheses is dr values (determined by the yields of isolated isomers).

As shown in Scheme 3, most of the corresponding products were obtained in moderate to good yields. *o*-MePh-EBX provided a lower yield than *m*-MePh-EBX and *p*-MePh-EBX probably

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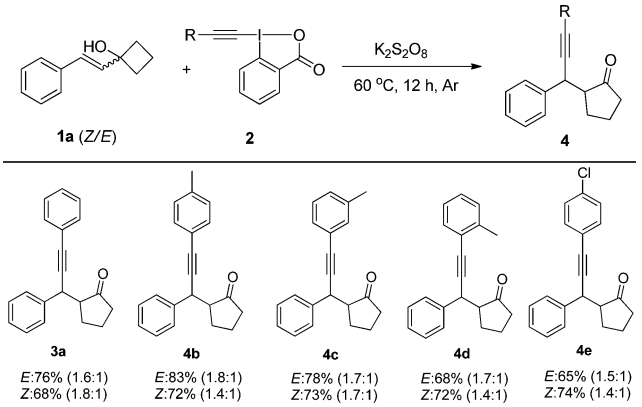
Scheme 3. Scope of Ethynylbenziodoxolones 2[a]



[a]Reaction conditions: **2** (0.2 mmol), **1a** (3.0 equiv), $K_2S_2O_8$ (4.0 equiv), CH_3CN (1 mL)/H_2O (1 mL) under an argon atmosphere at 60 °C for 12 h. Yield of isolated product. Number in parentheses is dr values (determined by the yields of isolated isomers).

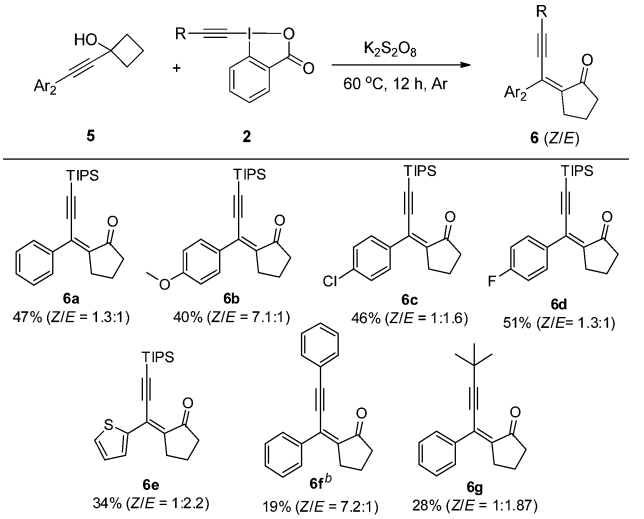
because of the steric hindrance (**4d** (*E*) vs **4b** (*E*) and **4c** (*E*)). In addition, we studied reactions between the substrates of *Z*/*E* configuration with various EBX. We found that substrates with either *Z* or *E* configuration could give the products in moderate to good yields, and the reaction was not sensitive to the substituents of EBX when the substrates with *Z* configuration participated in the reaction.

As far as we know, the metal-free ring expansion reaction of alkynyl cyclobutanols has not been reported yet.[15] Encouraged by the above results obtained for the vinylcyclobutanol, we further explored the reaction between the cyclobutanols bearing various ethynyl groups and ethynylbenziodoxolones. We were pleased to find that the cascade alkynylation/ring expansion reaction could proceed smoothly under slightly modified conditions,[16] which provided a straightforward route to synthesize ene-yne-carbonyl compounds (Scheme 4). Remarkably, 1-(thiophen-2-ylethynyl)cyclobutanol (**6e**) was successfully applied to this transformation, giving the heterocycle-substituted ene-yne-carbonyl compound in synthetically useful yields. The reactions between Ph-EBX or *t*-Bu-EBX and 1-(phenylethynyl)cyclobutanol gave the corresponding products in lower yields (**6f** and **6g**).

The products obtained here are highly functionalized with carbonyl and alkynyl groups, which could be readily converted into complex organic structures. We further performed subsequent transformations to explore the versatility of this method. As shown in Scheme 5, product **3a** could be converted to the corresponding hydrazine **7** and oxime **10** in good yields, and oxime derivatives are well-known potential precursors for the Beckmann rearrangement. It is worth mentioning that the corresponding hydrazine **7** realized a cyclization to afford pyridazine **8**, which could be further isomerized to pyridazine **9**. Compound **9** is the analogue of important monoamine oxidase-A (MAO-A) and MAO-B inhibitors, which are valuable antidepressant agents and useful as co-adjuvants in the treatment of Parkinson's disease, respectively.[17] These results show the transformation diversity of the β-alkynylated cyclopentanones and their potential in organic synthesis as useful intermediates.

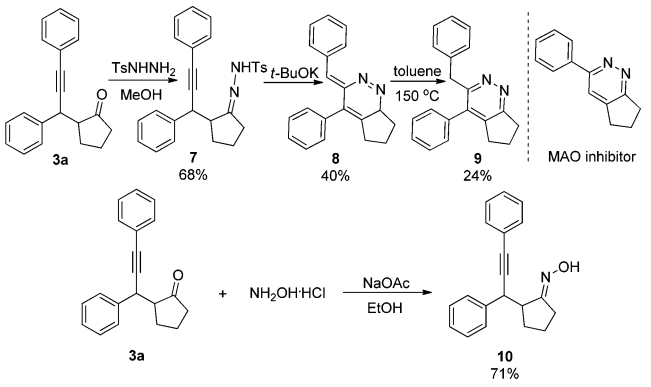
To gain mechanistic insight into the reaction, a controlled experiment was performed. The addition of the radical scavenger TEMPO significantly decreased the yield of the model reaction, and the trapped product **11** was detected by HR-MS (Scheme 6).

Scheme 4. Scope of Ethynylcyclobutanols 5[a]

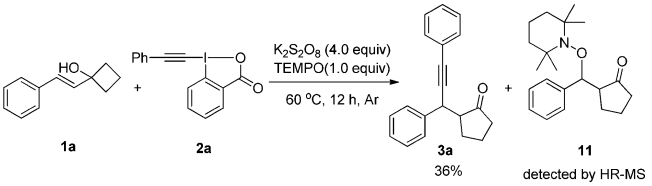


[a]Reaction conditions: **5** (0.2 mmol), **2** (3.0 equiv), $K_2S_2O_8$ (4.0 equiv), CH_3CN (1 mL)/H_2O (1 mL) under an argon atmosphere at 60 °C for 12 h. Yield of isolated product. Number in parentheses is the ratio of *Z*/*E* configuration of products (determined by NMR analysis). [b]Reaction conditions: **2** (0.2 mmol), **5** (3.0 equiv), $K_2S_2O_8$ (4.0 equiv), acetone (1 mL)/H_2O (1 mL) under an argon atmosphere at 60 °C for 12 h.

Scheme 5. Derivatization of 3a



Scheme 6. Radical Inhibition Experiment



This result indicates that the reaction most likely proceeds via a radical pathway. Subsequently, a possible mechanism is proposed in Scheme 7. First, an oxygen-centered radical species **A** is generated from 1-styrylcyclobutanol in the presence of $K_2S_2O_8$. Then, radical migration/ring expansion occur to form the radical intermediate **B**, which adds to EBX to form an intermediate **C**. β-Elimination of radical **C** affords the desired product accompanied by the formation of a benziodoxolonyl radical, which is further transformed to 2-iodobenzoic acid via a reduction−protonation sequence.

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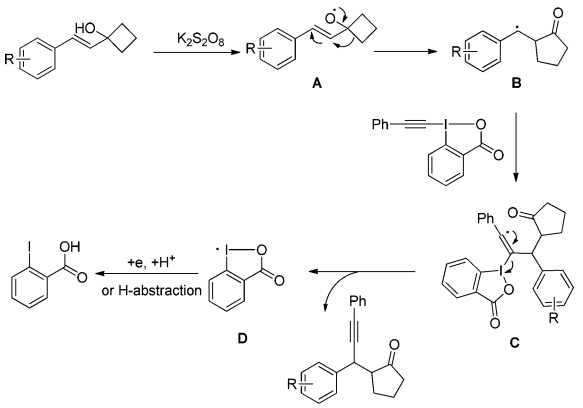
Scheme 7. Proposed Reaction Mechanism



In summary, we have developed the first alkynylation/ring expansion rearrangement of vinylcyclobutanol by using ethynylbenziodoxolones. The reaction proceeds under mild conditions without metal catalyst via a radical mechanism to afford a variety of β-alkynylated cyclopentanone derivatives in moderate to good yields. Analogously, alkynyl cyclobutanols could also undergo this transformation, providing a new approach to substituted ene-yne-carbonyl compounds. The highly functionalized cyclopentanones obtained here would be very useful in biochemistry and synthetic chemistry to construct valuable scaffolds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01856.

Experimental details and spectral data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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