Tetrahedron Letters xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

$K_2S_2O_8$-promoted [2+2]-cycloaddition of benzyl-2-(3-hydroxypropynyl)-benzoates: A new route to polysubstituted cyclobutanes

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ARTICLE INFO

Article history:
Received 22 September 2016
Revised 22 October 2016
Accepted 25 October 2016
Available online xxxx

Keywords:
Allenylic esters
[2+2]-Cycloaddition
$K_2S_2O_8$
Cyclobutanes
Propargyl alcohols

ABSTRACT

An efficient and convenient metal-free [2+2]-cycloaddition of benzyl-2-(3-hydroxypropynyl)-benzoates via allene processes has been developed, which provides impressive access to fused cyclobutanes from easily accessed π-components. This transformation involved the cleavage of two C–O bonds, the formations of two C–O bonds and two C–C bonds and showed some advantages, including mild conditions and wide substrate scope.

Introduction

The cyclobutane skeleton as a key structural element is found in biologically active natural product and pharmaceutical chemistry such as pipercyclobutanamide **A** (**1**), piperarborenine **D** (**2**), or Procoralan **3** (Fig. 1) [1]. Therefore, much attention has been paid to developing simple and effective methods for the synthesis of cyclobutane compounds.

As one of the most straightforward approaches, the [2+2]-cycloaddition have been extensive studied for the construction of diverse cyclobutanes. To date, many protocols was reported involving the π-electronic systems of olefins [2], allenes [3], alkadienes [4] or alkynes [5] in the presence of transition metal [6], chiral ligands [7], auxiliaries [8], Brønsted or Lewis acid [9]. In 2006, Kitagaki developed an elegant method for the synthesis of cyclobutanes from benzene-bridged bis(propargyl alcohols) via allene intermediates (Scheme 1a) [10]. In 2009, Tejedor synthesized cyclobutanes by a tertiary amine-catalyzed reaction involving 1,2-diketones and terminal conjugated acetylides, which appears to be an environmentally friendly method (Scheme 1b) [11]. In 2011, Chan reported the 1,3-migration/[2+2] cycloaddition of 1,7-enyne benzoates using Au(I) catalysis to provide the corresponding cyclobutane products (Scheme 1c) [12]. Although these methods have made important contribution to the synthesis of cyclobutanes, they still suffer from limited substrate scopes, harsh reaction conditions, low regioselectivity and the use of transition metal catalysts, the toxic and high cost of the reagent. Thus, further developments for more practical and efficient, high regioselectivity four-membered ring cyclization methodologies are quite desired. Herein, we have reported an efficient and convenient $K_2S_2O_8$-promoted [2+2] cycloaddition of benzyl-2-(3-hydroxypropynyl)-benzoates for the synthesis of polysubstituted cyclobutanes.

Results and discussion

At the outset of our investigation, we selected benzyl-2-(3-hydroxypropynyl)-benzoates (**1a**) as model substrate in the presence of 2.0 equiv $K_2S_2O_8$ in MeCN at 60 °C for 10 h. Then, the desired cyclobutane **2a** was isolated in 88% yield (Table 1, entry 1). The structure of the representative product **2a** was determined by X-ray crystallographic analysis (see the Supporting information) [13]. Further investigation showed that $Na_2S_2O_8$ and $(NH_4)_2S_2O_8$ were also effective for this cycloaddition and the desire product **2a** were obtained in 78% and 65% yields, respectively (entries 2 and 3). Next, several solvents such as THF, dioxane and DMF were screened and no significant improvements were observed (entries 3–9). Changing the amount of $K_2S_2O_8$ was less effective to the yields (entries 10 and 11). In addition, we also tested the effect

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http://dx.doi.org/10.1016/j.tetlet.2016.10.098
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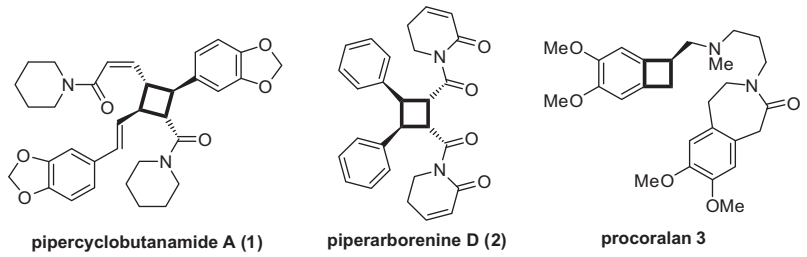
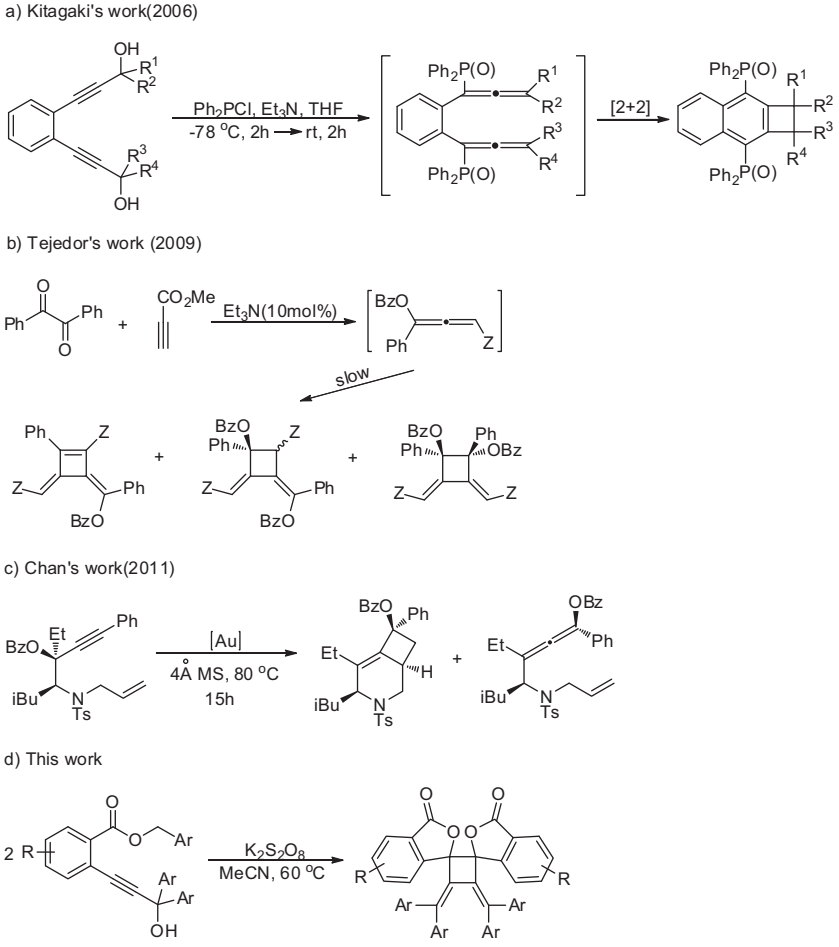


Figure 1. Examples of cyclobutanes in natural products and pharmaceutical chemistry.



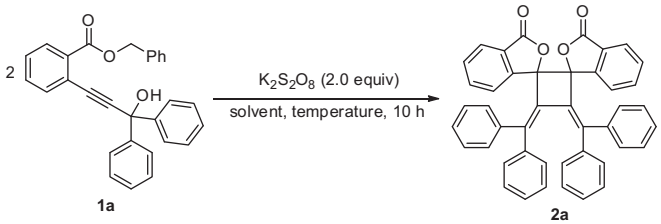
Scheme 1. The [2+2]-cycloaddition of allene intermediates for the synthesis of cyclotubanes.

of temperature. The obtained results revealed that lower or higher temperatures were not beneficial to the transformation.

With the optimal conditions in hand, the scope of the reaction was examined, as depicted in Table 2. We first investigated the reaction of substrate **1b** with isopropyl group instead of benzyl group under the optimized conditions, but the yield of the desired product **2a** greatly decreased. This might be because of the weaker nucleophilicity of the oxygen of the carbonyl group on isopropyl ester. Subsequently, we examined the electronic and steric effects of the substituents on R^2 of benzyl benzoate. It was found that substrates bearing either electron-withdrawing or electron-donating substituents reacted well. However, substrate **1c** with a methoxyl on the C-4 position of the aryl group showed better efficiency than substrate **1j** with a nitro substituent (**2c** vs **2j**). Remarkably, the cyclobutane product **2e** having a bromo group was obtained in 78% yield, which could be further elaborated by palladium-catalyzed processes. Furthermore, we examined the electronic effects of the substituents on the aromatic ring adjacent to the hydroxyl group. An electron-withdrawing (F) substituent on the aryl group afforded the corresponding product **2s** in 80% yield, but an electron-donating (OMe) substituent only resulted in a 46% yield of the product **2p**. We hypothesized that the electrophilicity of the allenolic cation intermediate was decreased in the latter case. The substrate **1t** with a methoxy and fluoro substituents was subjected to the optimum conditions, and the desired product **2t** was produced in low yield along with several unknown by-products.

Please cite this article in press as: Zhu H.-T., et al.. Tetrahedron Lett. (2016), http://dx.doi.org/10.1016/j.tetlet.2016.10.098

Table 1
Optimization study for the [2+2]-cycloaddition.[a]



Entry	Promotor	Solvent	Temperature (°C)	Yield (%)[b]
1	$K_2S_2O_8$	MeCN	60	88
2	$Na_2S_2O_8$	MeCN	60	78
3	$(NH_4)_2S_2O_8$	MeCN	60	65
4	$K_2S_2O_8$	THF	60	Trace
5	$K_2S_2O_8$	Toluene	60	Trace
6	$K_2S_2O_8$	$CHCl_3$	60	Trace
7	$K_2S_2O_8$	1,4-Dioxane	60	25
8	$K_2S_2O_8$	DMF	60	21
9	$K_2S_2O_8$	DMSO	60	<5
10[c]	$K_2S_2O_8$	MeCN	60	80
11[d]	$K_2S_2O_8$	MeCN	60	87
12	$K_2S_2O_8$	MeCN	rt	nr
13	$K_2S_2O_8$	MeCN	80	79

[a] Unless noted, all reactions were performed with **1** (0.2 mmol), $K_2S_2O_8$ (2.0 equiv), and solvent (2.0 mL) under air for 10 h.
[b] Isolated yield.
[c] $K_2S_2O_8$ (1.0 equiv).
[d] $K_2S_2O_8$ (3.0 equiv).

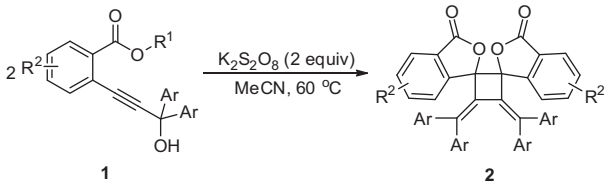
Specially, the reaction of benzyl-2-(9-hydroxy-9*H*-fluorenethynyl) benzoate **1v** could also give the polycyclic product **2v** in good yield.

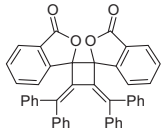
To gain insights into the mechanism of this reaction, we used $KHSO_4$ instead of $K_2S_2O_8$ to promote this reaction of **1a**, and the cyclobutane **2a** was obtained in 64% yield (Scheme 2, Eq. 1). In addition, 2,2,4,4-tetramethyl-1-piperidinyloxy (TEMPO, 2 equiv), and 2,6-di-*tert*-butyl-p-cresol (BHT, 2 equiv) as radical scavengers was employed to the [2+2]-cycloaddition of **1a** under standard reaction conditions (Scheme 2, Eqs. 2 and 3). Experimental results demonstrated that the [2+2]-cycloaddition of **1a** was only suppressed by TEMPO. We speculated that the interaction of $K_2S_2O_8$ with BHT may generate the acidic $KHSO_4$, which could active the hydroxy of **1a** to produce the allene intermediate.

On the basis of the results obtained above, a tentative mechanism was proposed in Scheme 3. Initially, sulfate radical anion ($.OSO_3^-$), generated in situ from the process thermolysis of $K_2S_2O_8$, activated the hydroxy of **1a** to afford HSO_4^- which could ionized a hydrion. Subsequently, the proton of HSO_4^- induced the losing of the hydroxy of **1a** was followed by nucleophilic attack by the oxygen of the carbonyl group on the alkynyl to obtain the allenylic ester **A** along with benzyl alcohol. Ultimately, the intermolecular dimerization of the allenylic ester **A** afforded the highly substituted cyclobutane **2a** probably through the concerted [$\pi_{2s} + \pi_{2a}$] or radical process [14].

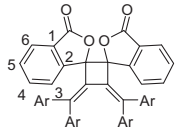
In conclusion, we have developed a metal-free and effective method for the synthesis of polysubstituted cyclobutanes from readily available benzyl-2-(3-hydroxypropynyl)-benzoates involving allenylic ester intermediates. The advantages of this cycloaddition include environmentally friendly conditions, the wide range of substrate scope and high regioselectivity. Application of symmetric cyclobutane derivatives to complex polycyclic compounds and axis chiral ligands is on the way.

Table 2
[2+2]-cycloaddition of propargyl alcohols **1a**–**1v** catalyzed by $K_2S_2O_8$.[a]

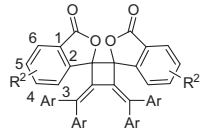




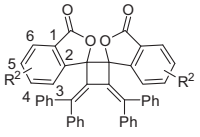
2a (86%, based on the reaction of **1a** bearing a benzyl group on R^1)
2a (30%, based on the reaction of **1b** bearing a isopropyl group on R^1)



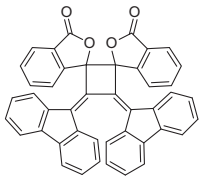
2p: Ar = 4-OMe-C_6H_4 (46%)
2q: Ar = 4-Me-C_6H_4 (62%)
2r: Ar = 4-Cl-C_6H_4 (71%)
2s: Ar = 4-F-C_6H_4 (80%)



2t: R^2 = 5-OMe, Ar = 4-F-C_6H_4 (29%)
2u: R^2 = 4-NO_2, Ar = 4-Cl-C_6H_4 (63%)[b]

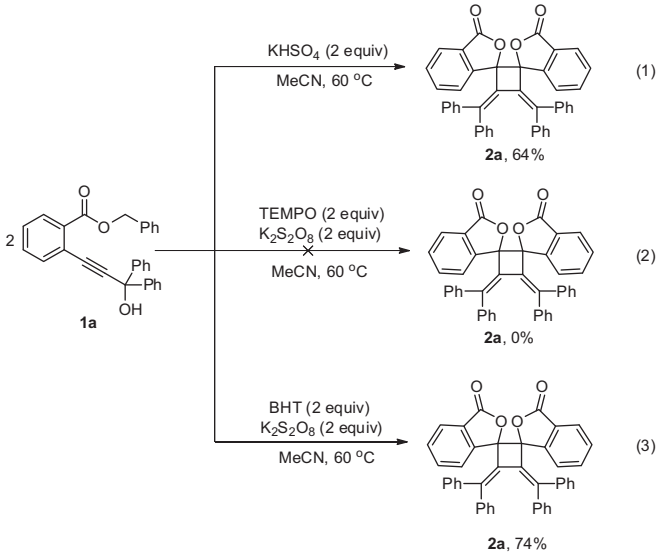


2c: R^2 = 5-OMe (79%)
2d: R^2 = 5-Me (64%)
2e: R^2 = 5-Br (78%)
2f: R^2 = 5-Cl (74%)
2g: R^2 = 5-F (80%)
2h: R^2 = 4-Cl (76%)[b]
2i: R^2 = 4-F (77%)
2j: R^2 = 4-NO_2 (55%)[b]
2k: R^2 = 6-Cl (67%)
2l: R^2 = 6-F (81%)
2m: R^2 = 6-Me (68%)
2n: R^2 = 4,5-OMe (73%)
2o: R^2 = 4,5-F (82%)

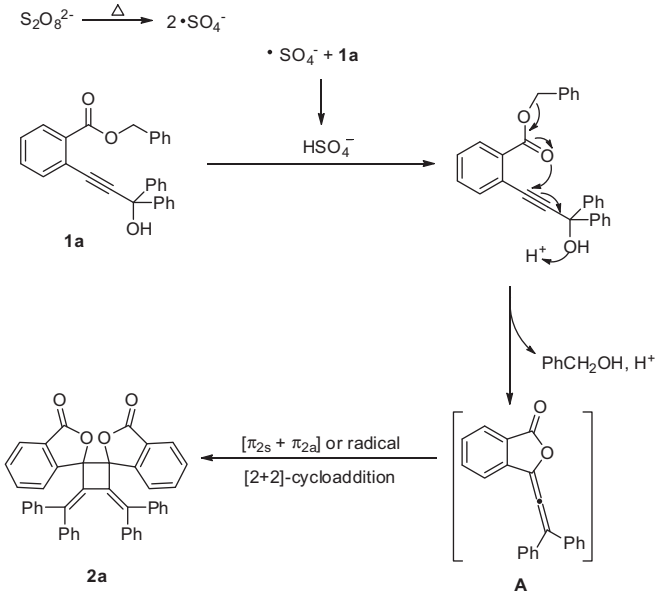


2v (79%)

[a] All reactions were performed on 0.2 mmol **1** with 2.0 equiv $K_2S_2O_8$ in MeCN (2 mL) at 60 °C under air for 7–15 h.
[b] 2.0 equiv $Na_2S_2O_8$ were used.



Scheme 2. Preliminary Mechanism Study.



Scheme 3. Proposed Mechanism.

Acknowledgments

We gratefully acknowledge the financial support of this work by the Education Department of Shaanxi Province Key Laboratory Project (15JS006), Ph.D. scientific research projects of Baoji University of Arts And Sciences (ZK15045 and ZK16060), and a China Postdoctoral Science Foundation funded project (2016M592826).

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.10.098.

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[13] CCDC 1422313 (**2a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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