



K₂S₂O₈-promoted [2+2]-cycloaddition of benzyl-2-(3-hydroxypropynyl)-benzoates: A new route to polysubstituted cyclobutanes



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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.

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Introduction

The cyclobutane skeleton as a key structural element is found in biologically active natural product and pharmaceutical chemistry such as pipericyclobutanamide **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 K₂S₂O₈-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 K₂S₂O₈ 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 Na₂S₂O₈ and (NH₄)₂S₂O₈ were also effective for this cycloaddition and the desired 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 K₂S₂O₈ was less effective to the yields (entries 10 and 11). In addition, we also tested the effect

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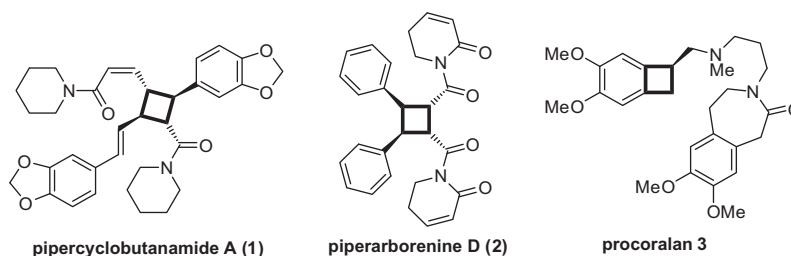
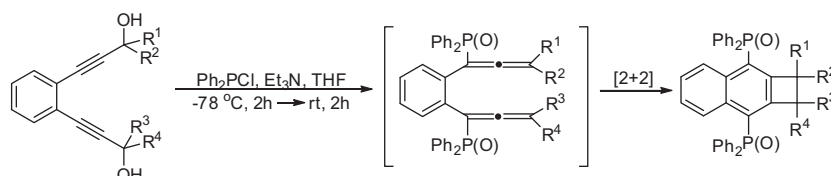
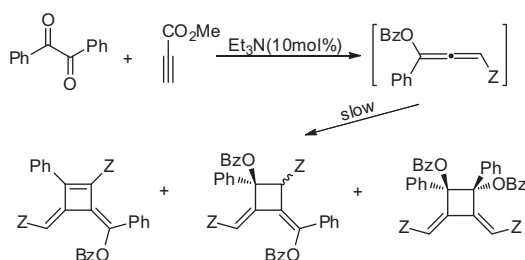


Figure 1. Examples of cyclobutanes in natural products and pharmaceutical chemistry.

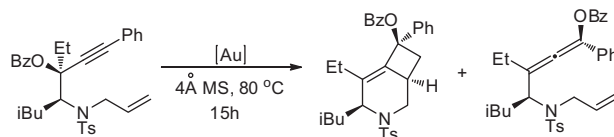
a) Kitagaki's work(2006)



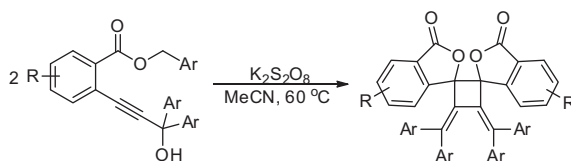
b) Tejedor's work (2009)



c) Chan's work(2011)



d) This work



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

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.

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