Organic LETTERS

Letter

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# Synergistic Acid-Promoted Synthesis of Highly Substituted Butenolides via the Annulation of Keto Acids and Tertiary Alcohols

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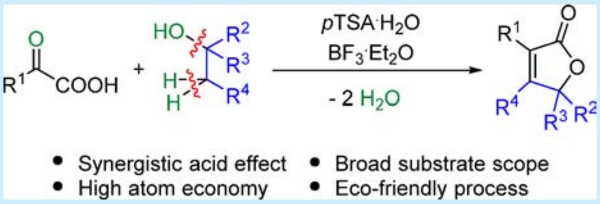
S *Supporting Information*

**ABSTRACT:** An efficient and practical approach to highly substituted butenolides via the annulation of keto acids and tertiary alcohols is described. The synergistic effect provided by the combination of Lewis and Brønsted acids is crucial to the reaction outcome. A variety of highly substituted butenolides are readily produced in synthetically useful yields. Water is the only waste from the reaction, therefore making it an environmentally benign and atom-economical process for butenolide synthesis.



Butenolide structural motifs are widely found in natural products and numerous compounds with biological activities.[1] For example, the most common and important butenolide is ascorbic acid (vitamin C);[1a] triptolide and tripdiolide are butenolide-containing diterpenoid triepoxides with significant antileukemic activity isolated from *Tripterygium wilfordii*, which has been long used as a traditional medicine in China;[1b,c] and Ianthellidone G and H are candidates of BACE inhibitors isolated from a southern Australian marine sponge, *Ianthella* sp. (Figure 1).[1g] Butenolides also frequently serve as versatile synthetic building blocks for the construction of complex molecules.[2] Thus, facile access to diverse butenolides is of considerable significance in organic and medicinal synthesis. In this scenario, an efficient approach to polysubstituted butenolides with broad diversity is highly desirable.

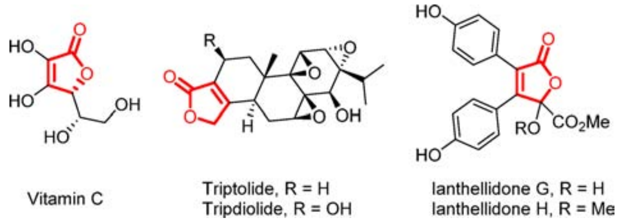


**Figure 1.** Natural products including a butenolide structural motif.

The synthesis of butenolides has made great progress in the past decade.[3−16] Generally, the most common strategy to build up butenolide rings relies on intramolecular cyclization.[3−9] However, these methods have some limitations, e.g., the use of expensive transition-metal catalysts (Rh, Pd, etc.) or complicated precursors that are sometimes hard to make, especially for the construction of multisubstituted butenolides. Herein we describe an efficient and practical approach to highly substituted butenolides via the annulation of keto acids and tertiary alcohols. The synergistic effect produced by the combination of Lewis and Brønsted acids is crucial to the reaction outcome.[17] A variety of highly substituted butenolides are obtained from readily available keto acids and tertiary alcohols. Water is the only waste from the reaction, thus making it an environmentally benign and atom-economical process for the butenolide synthesis.

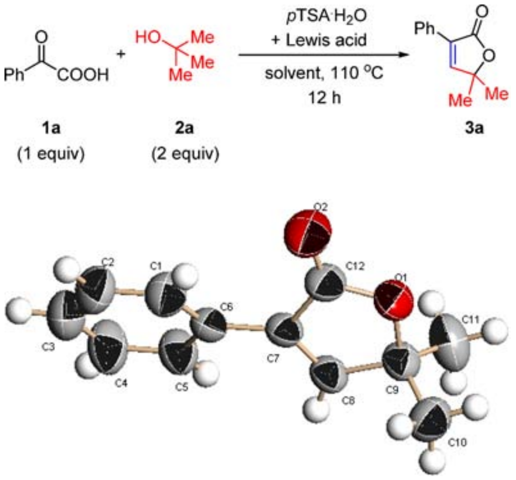
At the outset, the reaction parameters were systematically surveyed (Table 1). In the presence of 2 equiv of *p*TSA, only aromatic solvents led to the expected product **3a** (entries 1−3); other solvents entirely retarded the reaction (entries 4−8). The structure of **3a** was unambiguously assigned by single-crystal X-ray analysis. With xylene as the solvent of choice, we then assessed the effect of additives. It was found that the addition of various Lewis acids could improve the reaction outcome. While a series of metallic Lewis acids gave the product **3a** in moderate yields (entries 9−17), the use of 20 mol % $BF_3 \cdot Et_2O$ significantly increased the chemical yield to 92% (entry 18). The reaction time could be reduced to 3 h without compromising the reaction yield (entry 19). Tuning the amounts of tertiary alcohol to 1.5 equiv and $p$TSA·$H_2O$ to 2.5 equiv slightly improved the chemical yield (entry 20).

With the optimized reaction conditions in hand, we turned to an evaluation of the generality and limitations of this protocol (Scheme 1). Initially, a variety of keto acids were examined (**3a−q**). Both electron-rich and -deficient keto acids were tolerated under the reaction conditions; in general, the former gave better yields than the latter. However, the *p*-methoxy-substituted keto acid resulted in a surprisingly moderate yield (**3c**). The steric hindrance of keto acids exhibited a remarkable

**Received:** October 19, 2015
**Published:** November 9, 2015

DOI: 10.1021/acs.orglett.5b03026
*Org. Lett.* 2015, 17, 5710−5713

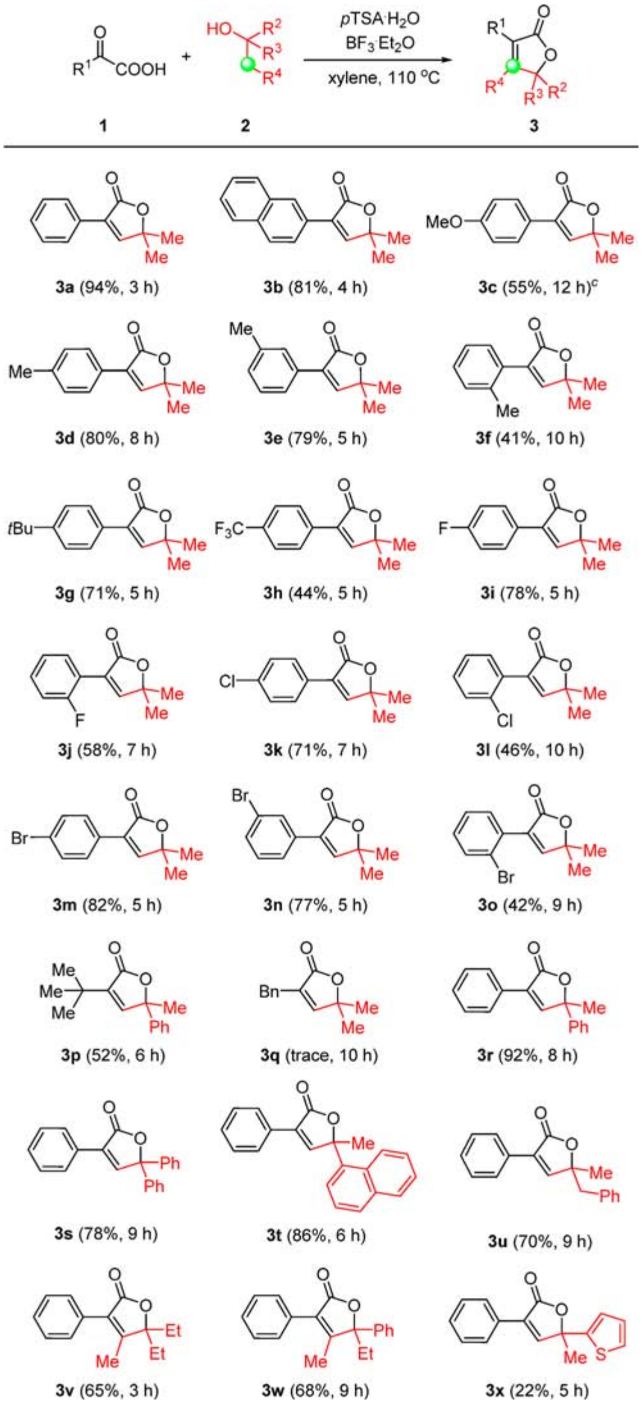
### Table 1. Survey of the Reaction Conditions[a]



| entry | solvent | Lewis acid | yield (%)[b] |
|---|---|---|---|
| 1 | toluene | – | 44 |
| 2 | xylene | – | 45 |
| 3 | mesitylene | – | 20 |
| 4 | dioxane | – | 0 |
| 5 | DMF | – | 0 |
| 6 | DMSO | – | 0 |
| 7 | acetonitrile | – | 0 |
| 8 | $CCl_4$ | – | 0 |
| 9 | xylene | $FeCl_3$ | 60 |
| 10 | xylene | $FeSO_4\cdot 7H_2O$ | 56 |
| 11 | xylene | $Gd(OTf)_3$ | 51 |
| 12 | xylene | $ZnCl_2$ | 49 |
| 13 | xylene | $InCl_3$ | 48 |
| 14 | xylene | $AlCl_3$ | 67 |
| 15 | xylene | $Cu(OTf)_2$ | 45 |
| 16 | xylene | $Sc(OTf)_3$ | 65 |
| 17 | xylene | $Sm(OTf)_3$ | 66 |
| 18 | xylene | $BF_3\cdot Et_2O$ | 92 |
| 19[c] | xylene | $BF_3\cdot Et_2O$ | 92 |
| 20[d] | xylene | $BF_3\cdot Et_2O$ | 94 |

[a] **1a** (0.3 mmol), **2a** (0.6 mmol, 2 equiv), *p*TSA·$H_2O$ (0.6 mmol, 2 equiv), and Lewis acid (0.06 mmol, 0.2 equiv) in 2 mL of solvent at 110 °C. [b] Yields of isolated products. [c] 3 h. [d] 1.5 equiv of **2a**, 2.5 equiv of *p*TSA·$H_2O$, 3 h.

### Scheme 1. Substrate Scope[a,b]

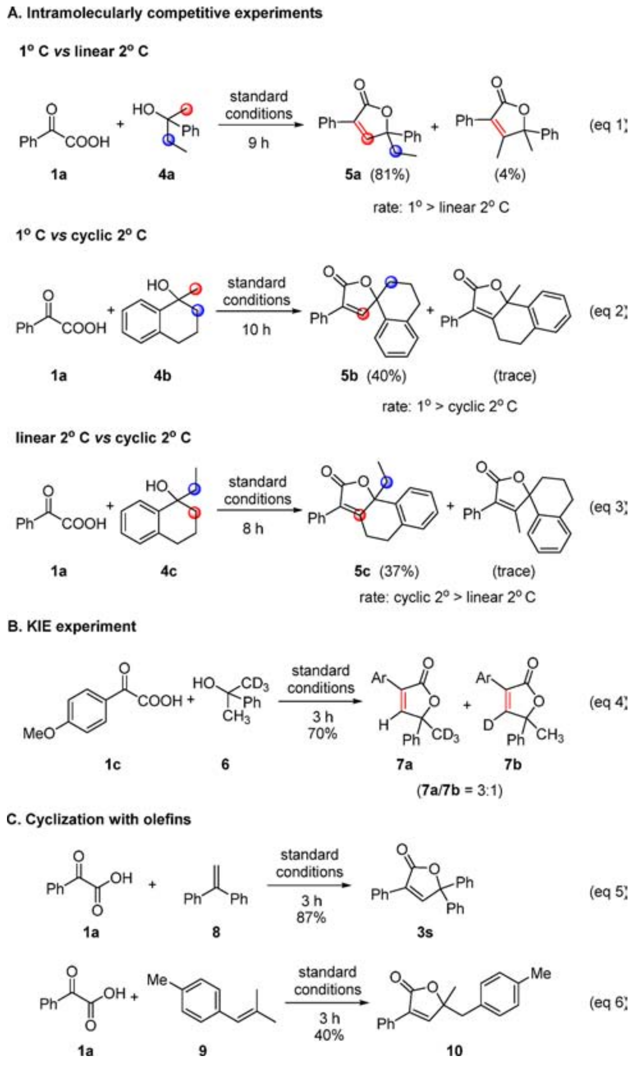


[a] **1** (0.3 mmol), **2** (0.45 mmol, 1.5 equiv), *p*TSA·$H_2O$ (0.75 mmol, 2.5 equiv), and $BF_3\cdot Et_2O$ (0.06 mmol, 0.2 equiv) in 2 mL of xylene at 110 °C. [b] Yields of isolated products are shown. [c] 70 °C.

impact on the reaction (**3f**, **3l**, and **3o**), as the congested *ortho*-substituted substrates usually provided lower yields than the *para*- and *meta*-substituted ones. Halogenated keto acids were apt (**3i**–**3o**), which is noteworthy since the introduction of halides, in particular bromide, provides a platform for further product manipulation via cross-coupling. While *tert*-butyl keto acid gave the desired product in synthetically useful yield (**3p**), benzyl keto acid was incompatible with the reaction conditions (**3q**). This could be attributed to the presence of the $\alpha$-H adjacent to the keto acid, although the exact reason is currently unclear. Moreover, glyoxylic acid and oxalic acid were also incompatible with the reaction conditions. Next, an array of tertiary alcohols were investigated. In addition to $^t$BuOH, both mono- and diaryl tertiary alcohols were suitable substrates, giving the corresponding butenolides (**3r** and **3s**) in good yields. The substrate with bulky naphthyl instead of phenyl also delivered a high yield of the product (**3t**). Notably, a unique regioselectivity was observed in the reaction when an unsymmetrical tertiary trialkyl alcohol was applied (**3u**). In addition to methyl, the cyclization of methylene also proceeded smoothly to furnish the fully substituted butenolides in useful yields (**3v** and **3w**). The reaction with heteroaryl substrates such as a thienyl-substituted tertiary alcohol resulted in a low yield (**3x**).

To gain mechanistic insight into the cyclization reaction, several experiments were performed. First, an intramolecularly competitive reaction was conducted (Scheme 2A). The transformation provided good differentiation between different

**Scheme 2. Mechanistic Studies**


A. Intramolecularly competitive experiments

B. KIE experiment

C. Cyclization with olefins

types of carbon centers. Although the methylene readily underwent the cyclization in the cases of **3v** and **3w**, the reaction predominantly occurred at methyl rather than linear (**4a**) and cyclic (**4b**) methylene (Scheme 2A, eqs 1 and 2). In the example of **4c**, the reaction preferred cyclic methylene to linear methylene, affording the complexly bicyclic butenolide **5c** (Scheme 2A, eq 3). In a KIE experiment, the resulting 3:1 ratio of two deuterated butenolides (**7a** and **7b**) suggested that cleavage of the C−H bond of the tertiary alcohol might be the rate-limiting step in the overall transformation (Scheme 2B). On the basis of the experimental data and literature precedent,[18] we speculated that the reaction might go through the cyclization of an olefin intermediate generated by acid-promoted dehydration of the tertiary alcohol. However, the result of **3u** was unexpected and seemed to contradict this hypothesis, as the dehydration of 2-benzyl isopropanol was supposed to give as the major product the thermodynamically preferred trisubstituted internal alkene, which would lead to a different butenolide.[19] To test the hypothesis, we examined the direct interaction of keto acid **1a** with alkenes (Scheme 2C). The reaction of terminal alkene **8** gave the expected butenolide **3s** in high yield, thereby verifying the possibility of olefin-involved mechanism. Nevertheless, the reaction of internal alkene **9** generated the unexpected butenolide **10** derived from the terminal olefinic isomer of **9**, consistent with the result of **3u**.

A proposed mechanistic pathway is outlined in Figure 2. Initially, the acid-promoted dehydration of tertiary alcohol **2** leads to internal alkene intermediate **a**. In the presence of protic acid, **a** is partially isomerized to the less hindered terminal alkene **b**, which is ready to nucleophilically attack the activated keto acid **1**. The generated intermediate **c** rapidly cyclizes to give $\alpha$-hydroxybutyrolactone **d**, which can eventually result in butenolide **3** after dehydration.

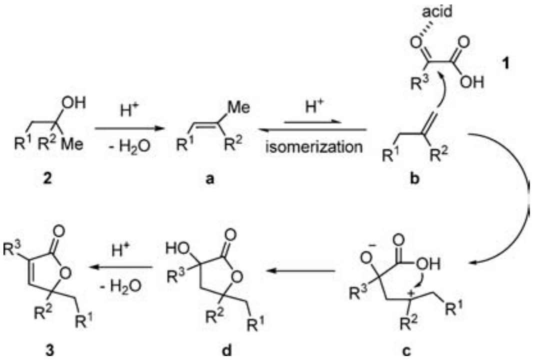
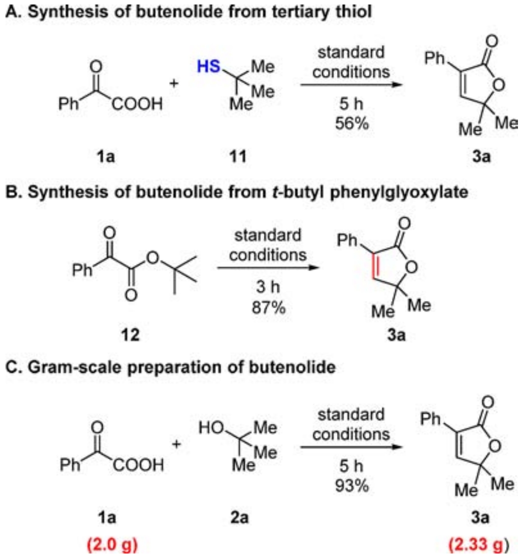


**Figure 2.** Plausible mechanistic pathway.

The protocol could be applied to other substrates for the formation of butenolides. For example, the use of tertiary thiol **11** in lieu of an alcohol under the same reaction conditions afforded butenolide **3a** in moderate yield (Scheme 3A). The reaction of *tert*-butyl phenylglyoxylate (**12**) also gave rise to butenolide **3a** in high yield (Scheme 3B). To demonstrate the practicability of the method, a gram-scale reaction was carried out. Reaction of 2.0 g of **1a** under the standard reaction conditions gave butenolide **3a** (2.33 g) within 5 h in 93% isolated yield (Scheme 3C).

**Scheme 3. Other Applications**


A. Synthesis of butenolide from tertiary thiol

B. Synthesis of butenolide from *t*-butyl phenylglyoxylate

C. Gram-scale preparation of butenolide

In summary, we have described an efficient and practical approach to highly substituted butenolides via the annulation of keto acids and tertiary alcohols. A variety of highly substituted butenolides were readily obtained in synthetically useful yields.

The reaction can be scaled up to gram quantities, demonstrating the practicability of the method. The reaction conditions can be further applied to the transformation of tertiary thiol or *tert*-butyl phenylglyoxylate to butenolide. Water is the only waste in the reaction, thus making it an environmentally benign and atom-economical process for butenolide synthesis.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03026.

Experimental details, compound characterization data, and NMR spectra (PDF)
X-ray crystallographic data for **3a** (CIF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

C.Z. is grateful for the financial support from Soochow University, the National Natural Science Foundation of China (Grant 21402134), the Natural Science Foundation of Jiangsu Province (Grant BK20140306), and the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD). We thank Dr. Xiaodi Yang of Fudan University for help with the single crystal X-ray analysis of compound **3a**.

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