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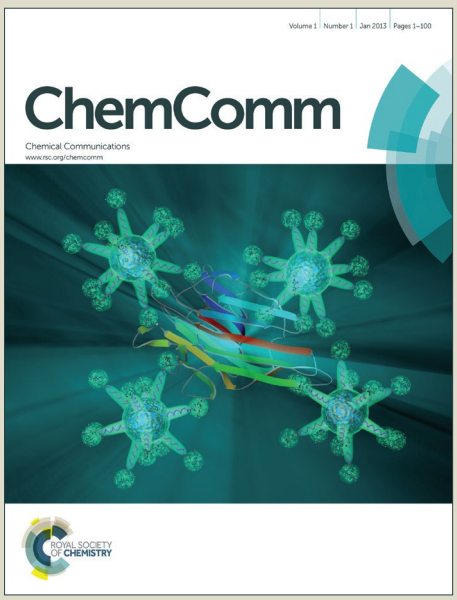

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Journal Name

COMMUNICATION

Synthesis of Highly Substituted γ-Hydroxybutenolides through the Annulation of Keto Acids with Alkynes and Subsequent Hydroxyl Transposition

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An efficient synthesis of highly functionalized γ-hydroxybutenolides through BF_3-catalyzed annulation of keto acids with alkynes is described. Many advantages such as the use of routine reagents, easy operation, and a 100% atom efficiency are demonstrated in the method. The reaction can be readily scaled up to gram quantities, offering a good practicality.

γ-Hydroxybutenolides are important structural motifs extensively found in natural products and have exhibited a wide range of biological activities. Ianthellidone G is isolated from a southern Australian marine sponge, *Ianthella sp.* and treated as a candidate of BACE inhibitors.[1] Moreover, a series of terpenoids from marine sponges, such as manoalide, cacospongionolides, and petrosaspongioides, have remarkably anti-inflammatory properties (Figure 1).[2] On the other hand, γ-hydroxybutenolides are versatile synthetic intermediates for the assembly of complex natural products and bioactive molecules.[3] Therefore, the rapid and efficient construction of highly functionalized γ-hydroxybutenolides is of considerable importance in both fields of synthetic and medicinal chemistry.

The construction of the five-membered lactone is the key step in the synthesis of γ-hydroxybutenolides, and has made a great progress over the past few decades. Among these methods, there are two common strategies: a) intermolecular aldol reaction between α-bromoketone and acetic acid followed by air oxidation (Scheme 1, eq 1),[4-8] and b) aldol condensation between γ-ketoester and aldehyde (Scheme 1, eq 2).[9-14] However, the former requires the use of preformed perishable α-bromoketones; the latter harnesses the multi-step prepared γ-ketoesters which are sometimes hard to make. Very recently, Shishido et al. reported the intermolecular carbonylative cycloaddition of aldehydes with

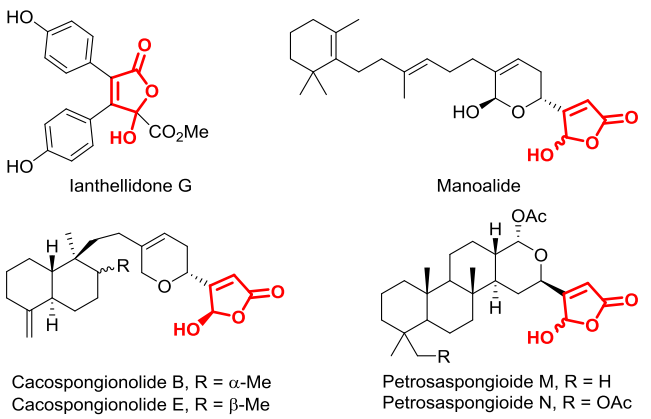

Figure 1. Natural products including γ-hydroxybutenolides structural motif.

alkynes, namely oxa-Pauson-Khand reaction (Scheme 1, eq 3).[15] Although this approach produced a variety of highly substituted γ-hydroxybutenolides in modest yields, the employment of harsh reaction conditions and costly transition-metal catalyst and ligand significantly limited its applications. Herein, we describe an efficient and practical approach to highly functionalized γ-hydroxybutenolides through the Lewis acid-catalyzed annulation of keto acids with alkynes (Scheme 1, eq 4). The transformation affords an atom efficiency of 100%, and only routine reagents are applied. Remarkably, the gram-scale preparation of γ-hydroxybutenolide explicitly illustrates the practicability of this protocol.

Recently, we disclosed the cyclization of keto acids with tertiary alcohols to generate butenolides, in which the combinational use of *p*TSA·H_2O and BF_3·Et_2O was crucial to the reaction outcome, and exhibited a good catalytic performance.[16] Inspired by these findings, we hypothesized that in the presence of acid catalyst, the annulation of keto acid **1** with alkyne **2** in lieu of tertiary alcohol would give a-hydroxylactone **4** as the expected product (Scheme 2).

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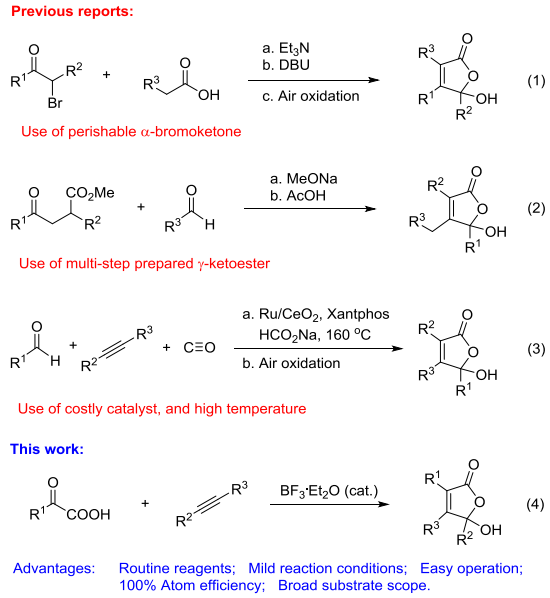
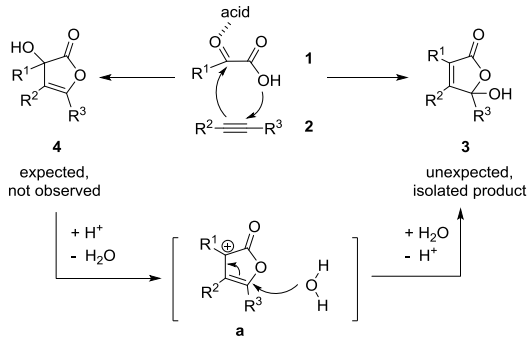


Scheme 1. Preparation of γ-Hydroxybutenolides

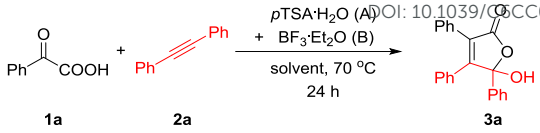
Surprisingly, the unexpected γ-hydroxybutenolide **3**, a hydroxyl-transpositional isomer of **4**, was generated in the reaction. Regarding the possibly mechanistic pathway, we postulated that after the formation of **4**, the acid-promoted protonation and dehydration of **4** led to the intermediate **a**. Subsequently, the cation-driven nucleophilic addition of H_2O to **a** gave rise to the product **3**.

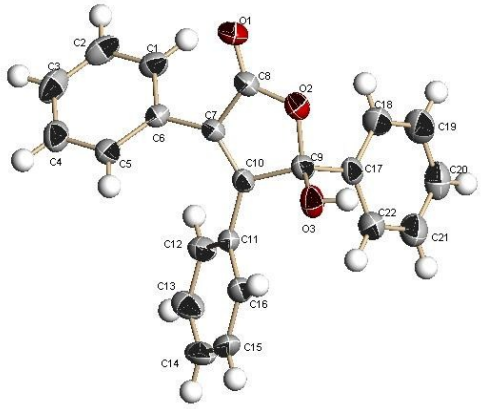
Encouraged by these preliminary results, we set out to optimize the reaction conditions for the annulation of keto acid **1a** with alkyne **2a** (Table 1). Initially, we examined different solvents in the presence of combined acids of *p*TSA·H_2O and BF_3·Et_2O (entries 1-9). Fluorobenzene was found to be the most efficient one, delivering a better yield than other solvents (entry 4). Raising the quantity of BF_3·Et_2O from 0.2 to 0.3 equiv appreciably improved the chemical yield of **3a** (entry 10). Finally, it was noted that *p*TSA·H_2O was unnecessary to the transformation, and singly using 30 mol % of BF_3·Et_2O could give the comparably high yield (entry 12). The structure of **3a** was unambiguously assigned by single crystal X-ray analysis.[17]



Scheme 2. Proposed Mechanism for the Annulation of Keto Acid with Alkyne

Table 1. Reaction Condition Survey [a]

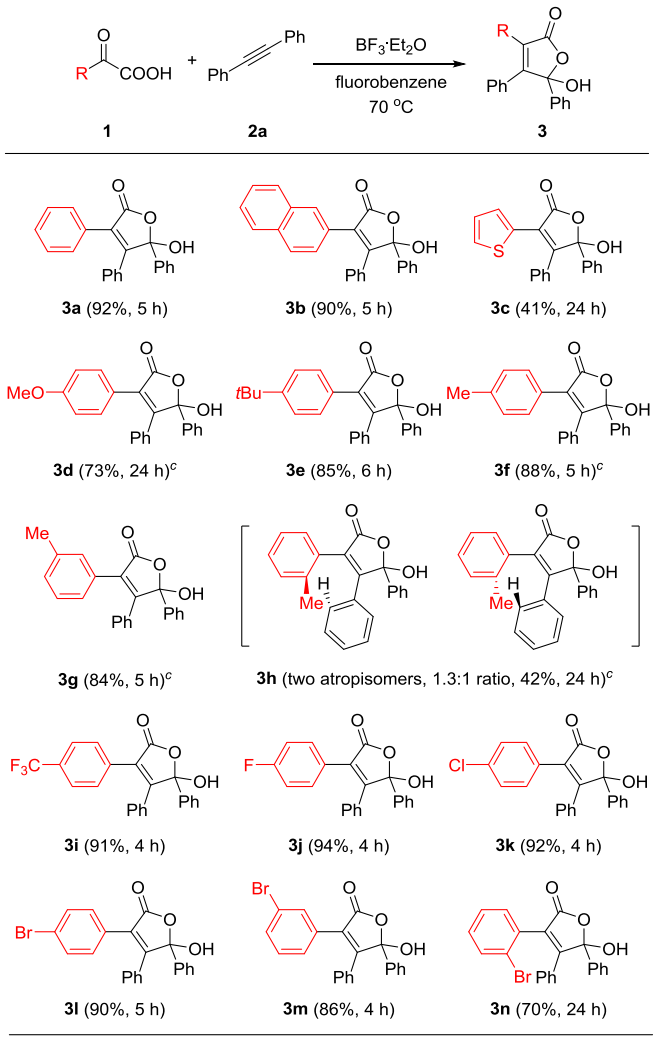




entry	solvent	ratio (**1a**: **2a**: A: B)	yield(%)[b]
1	toluene	1: 2: 2: 0.2	46
2	benzene	1: 2: 2: 0.2	76
3	chlorobenzene	1: 2: 2: 0.2	46
4	fluorobenzene	1: 2: 2: 0.2	78
5	DMF	1: 2: 2: 0.2	< 5
6	DMSO	1: 2: 2: 0.2	< 5
7	CH_3CN	1: 2: 2: 0.2	< 5
8	THF	1: 2: 2: 0.2	< 5
9	DCE	1: 2: 2: 0.2	54
10	fluorobenzene	1: 2: 2: 0.3	93
11	fluorobenzene	1: 2: 2: 0	< 5
12[c]	fluorobenzene	1: 2: 0: 0.3	92

[a] **1a** (0.3 mmol), **2a** (0.6 mmol, 2 equiv), *p*TSA·H_2O (as shown), and BF_3·Et_2O (as shown) in 2 mL solvent at 70 °C. [b] Yields of isolated product. [c] 5 h.

With the optimized reaction conditions in hand, we set about assessing the generality of this protocol. Firstly, we investigated a variety of keto acids (Scheme 3). Both electron-rich and deficient keto acids were compatible with the conditions, affording good chemical yields. While aryl keto acids were readily converted into the desired products (**3a** and **3b**), the reaction of heteroaryl keto acid was more sluggish and resulted in moderate yield (**3c**). The steric hindrance seemed to have considerable impact on the reaction outcome, as the *ortho*-substituted keto acids usually led to lower yields and longer reaction time (**3h** and **3n**). Notably, a pair of atropisomers of **3h** with 1.3:1 ratio was observed by NMR spectra at rt, and disappeared at 80 °C in DMSO. Even the substrate with strong electron-withdrawing group, such as CF_3,

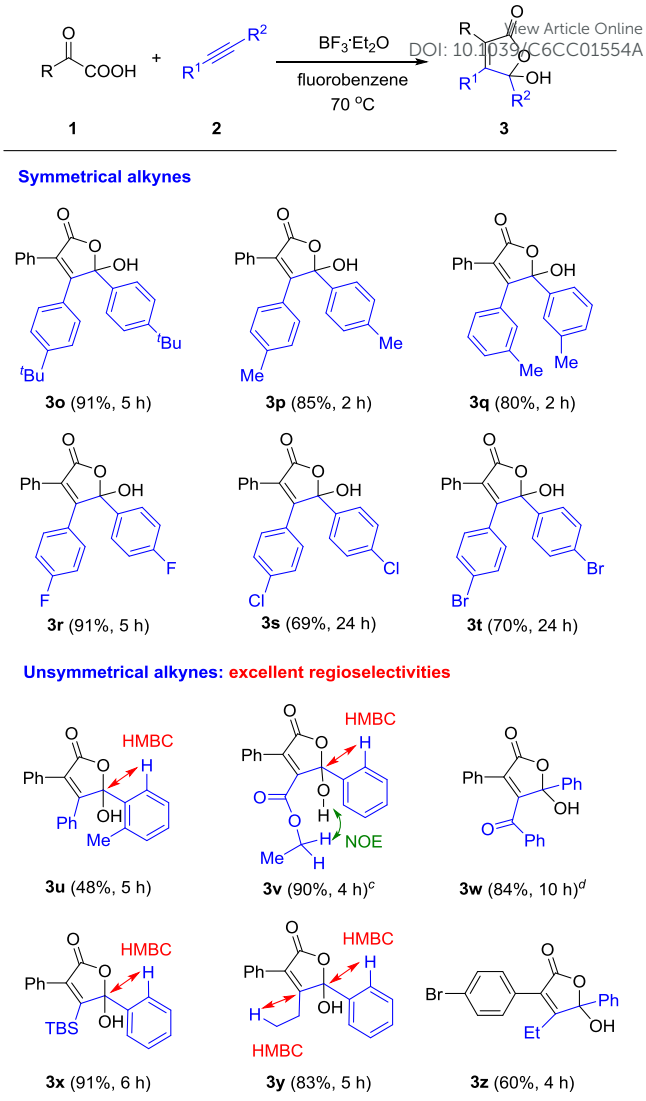


Scheme 3. Variation of Keto Acids [a,b]

[a] 1 (0.3 mmol), 2a (0.6 mmol, 2.0 equiv), and $BF_3{\cdot}Et_2O$ (0.09 mmol, 0.3 equiv) in 2 mL fluorobenzene at 70 °C. [b] Yields of isolated product. [c] $BF_3{\cdot}Et_2O$ (0.12 mmol, 0.4 equiv).

was well tolerated to give high yield (**3i**). The examples of **3l**-**3n** were noteworthy, since the presence of bromide provided the platform for later product modification through cross-coupling reactions. It should be mentioned that alkyl keto acids and glyoxylic acid were incompatible with the reaction conditions.

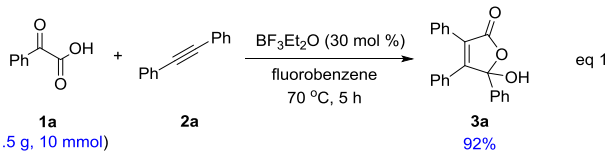
Afterward, we turned to evaluate the scope of alkynes (Scheme 4). Firstly, symmetrical diaryl acetylenes bearing either electron-donating or withdrawing groups were suitable substrates to afford the desired products in good yields (**3o**-**3t**). The reaction provided a precise discrimination for the steric hindrance. For example, the use of unsymmetrical diaryl acetylene led to a single adduct **3u**, in which the bulky *o*-tolyl group was positioned outside to avoid the steric repulsion from aryl keto acid. The annulation with the carbonyl-activated acetylenes also resulted in solely isomeric products (**3v** and **3w**). Notably, the unique regioselectivities were unexpectedly achieved even in the reaction with siyl- or alkyl-substituted phenylacetylenes (**3x**-**3z**).



Scheme 4. Variation of Alkynes [a,b]

[a] **1** (0.3 mmol), **2** (0.6 mmol, 2.0 equiv), and $BF_3{\cdot}Et_2O$ (0.09 mmol, 0.3 equiv) in 2 mL fluorobenzene at 70 °C. [b] Yields of isolated product. [c] $BF_3{\cdot}Et_2O$ (0.18 mmol, 0.6 equiv). [d] $BF_3{\cdot}Et_2O$ (0.12 mmol, 0.4 equiv).

The practicality of this method was demonstrated by the gram-scale reaction. Under the standard reaction conditions, 1.5 gram of phenyl keto acid **1a** (10 mmol) was readily converted into γ-hydroxybutenolide **3a** in 92% yield (eq 1).



In summary, a BF_3-catalyzed intermolecular annulation of keto acids with alkynes has been described. An unexpected hydroxyl transposition occurs after the annulation. A variety of highly functionalized γ-hydroxybutenolides are efficiently

obtained. The method demonstrates many advantages such as the use of routine reagents, easy operation, unique regioselectivity, and a 100% atom efficiency, and can be readily scaled up to gram quantities, thereby providing a practical approach for the synthesis of γ-hydroxybutenolides.

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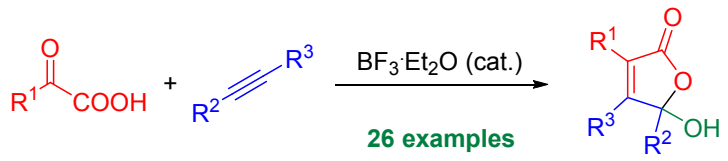

- 100% Atom efficiency
- Routine reagents
- Easy operation
- Broad substrate scope
- High product diversity

A BF_3-catalyzed, practical synthesis of highly functionalized γ-hydroxybutenolides with a 100% atom efficiency is described.