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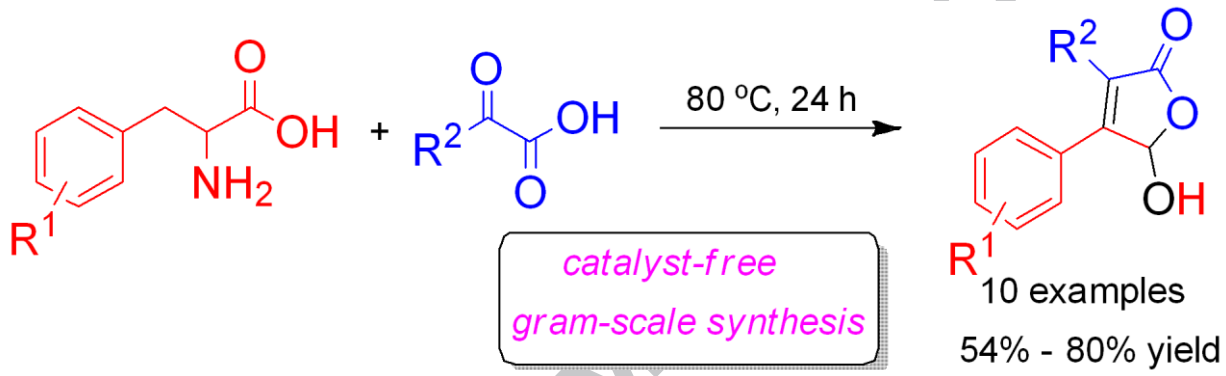

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One-pot gram-scale synthesis of γ-hydroxybutenolides through catalyst-free annulation of α-amino acids with α-keto acids in water

Zhiqing He[a] , Fang Fang[a] , Jianguang Lv[a] , and Jianmin Zhang[a,b,] *

[a]Department of Chemistry, Innovative Drug Research Center, Shanghai University, Shanghai 200444, China
[b]Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Science, Shanghai 200032, China

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ABSTRACT

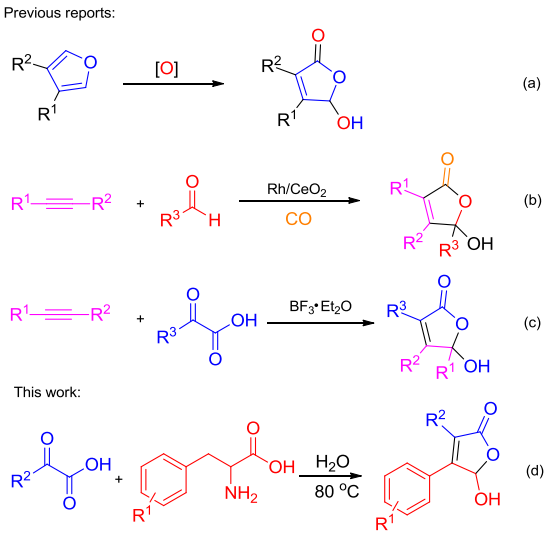
A one-pot gram-scale synthetic route for the preparation of γ-hydroxybutenolides via catalyst-free annulation of α-amino acids with α-keto acids in water is reported. The method shows many advantages such as readily available starting materials, mild reaction conditions, operational simplicity, acceptable yields, and requiring no extra catalysts or additions. Furthermore, the method is innocuous to the environment, also is valuable to industry.

Introduction

Butenolides are a sort of very important subunits in the structures of natural products and bioactive compounds, which exhibit physiological effects including antisepsis, anticancer, and antiphlogosis. Due to their using in medicine[1] and synthesis of natural products and bioactive molecules[2], butenolides are attracting wide attention in synthetic organic chemistry. As a consequence, several methodologies have been developed to synthesize these classes of compounds in literature.[3] The most direct method is via the oxidation of furans by oxygens under severe conditions (Scheme 1, route a).[4] For more specific examples, intermolecular [2+2+1] carbonylative cycloaddition of aldehydes with alkynes and subsequent oxidation to γ-hydroxybutenolides is achieved by ruthenium-catalyst (Scheme 1, route b).[5] As an interesting example, BF_3-catalyzed annulation of keto acids with alkynes produces butenolides with the carbonyl carbon of α-keto acids as the cyclization point (Scheme 1, route c).[6] Although some advances have been made in synthesis of butenolides and the analogues, these methods are unfriendly to the environment involving the use of expensive and toxic catalysts or organic solvents.

As well known, the utilization of water as a solvent is an aspect of Green Chemistry because of its benign environmental character.[7] In addition, compared with the various solvent alternatives in organic chemistry, water is very cheap and nontoxic.[8] Keeping this in our mind, we try to develop a Green strategy to construct γ-hydroxybutenolides. Herein, we report a one-pot gram-scale synthetic route of γ- hydroxybutenolides through catalyst-free annulation of α-amino acids and α-keto acids in water under mild reaction conditions (Scheme 1, route d). All the reactants abound in human body and participate in metabolism and structure transformation. Thus, the method is innocuous to the environment, but also is valuable to industry.

The γ-hydroxybutenolide products have never been reported except **3b** because of the difficulty in their syntheses. Even **3b** was reported to prepared by up to 6 steps in just 34% overall yield[9] or obtained through three steps in 25% overall yield[10].



Scheme 1 Literature approaches to butenolides and our design.

* Corresponding author. E-mail: jmzhang@shu.edu.cn (J. Zhang)

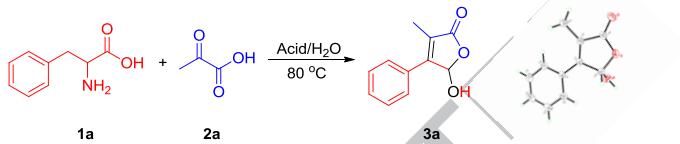
Resules and discussion

Initially, we chose the reaction of phenylalanine **1a** with pyruvic acid **2a** as the model reaction to screen the reaction conditions (Table 1). Phenylalanine **1a** was treated with pyruvic acid **2a** in the presence of acetic acid (HOAc) in H_2O (2 mL) at 80 °C for 24 h under air atmosphere. 5-hydroxy-3-methyl-4-phenylfuran-2(5H)-one **3a** was isolated in 15% yield (Table 1, entry 1). The structure of **3a** was unambiguously confirmed by single crystal X-ray diffraction analysis.[11] Increase of concentration could raise the isolated yield over the same reaction time (Table 1, entries 2, 3 and 4). When the loading of **2a** was increased to 10 equiv, the desired product **3a** was obtained in 64% yield. Efforts to reduce the amount of **2a** by replacing HOAc with $HClO_4$, CF_3COOH, $PhB(OH)_2$, $BF_3{\cdot}Et_2O$, p-toluenesulfonic acid (PTSA), or changing the solvent and molar ratio are proved fruitless(Table 1, entries 5-13). The highest yield of **3a** was achieved in the absence of HOAc (Table 1, entries 14). Increasing or reducing the loading of **2a** led to no improvement of yield either (Table 1, entries 15-16). Moreover, Slow addition of **2a**, prolonging the reaction time or increasing the reaction temperature could not further improve the yield of **3a** (Table 1, entries 18-19). Accordingly, the molar ratio of **1a**/**2a** as 1:10 and the reaction temperature as 80 °C were selected as the optimized reaction conditions (Table 1, entry 14).

With the optimized reaction conditions in hand, we started to investigate the substrate scope (Table 2). Firstly, we used various α-amino acids **1** to react with α-keto acids **2a**. Substrates with electron-donating or electron-withdrawing groups on the phenyl

Table 1

Optimization of the reaction conditions[a]



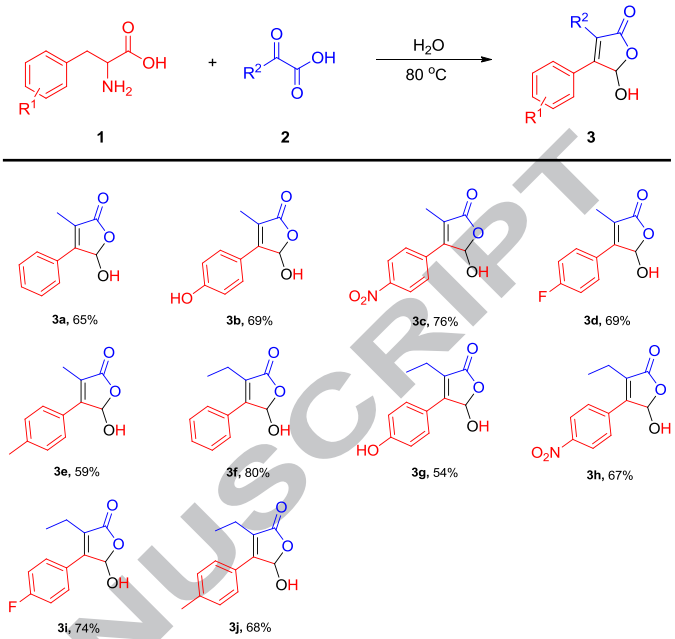
1a 2a 3a

Entry	Acid	Molar ratio[b]	T(°C)	Yield (%)[c]
1[d]	HOAc	1:3:1	80	15
2[e]	HOAc	1:3:1	80	25
3	HOAc	1:3:1	80	38
4	HOAc	1:10:1	80	64
5	$HClO_4$	1:3:1	80	35
6	CF_3COOH	1:3:1	80	34
7	$PhB(OH)_2$	1:3:1	80	32
8	$BF_3{\cdot}Et_2O$	1:3:1	80	24
9	PTSA	1:3:1	80	36
10[f]	HOAc	1:3:1	80	33
11[g]	HOAc	1:3:1	80	34
12	HOAc	1:3:2	80	35
13	HOAc	1:5:1	80	53
14	-	1:10:0	80	65
15	-	1:5:0	80	43
16[h]	-	1:20:0	80	63
17[i]		1:10:0	80	64
18	-	1:10:0	100	63
19	-	1:10:0	120	58

[a] Unless specified, all reactions were performed in 0.5 mL H_2O at 80 °C for 24 h under air. [b] Molar ratio refers to **1a**/**2a**/acid. [c] Isolated yield. [d] The solvent volume w as 2 mL. [e] The solvent volume was 1 mL. [f] The mixed solvent was H_2O and 1,4-dioxane (3:2). [g] The mixed solvent was H_2O and THF (3:2). [h] The reaction time was prolonged to 72 h. [i] Slow addition of **2a**.

Table 2

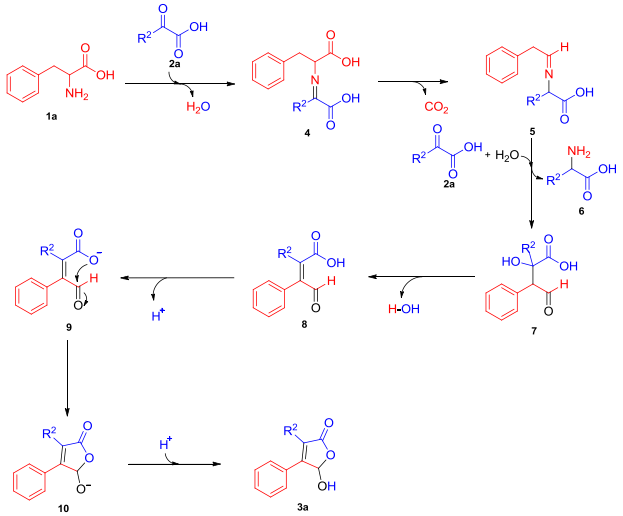
Substrate scope[a]



[a] Unless otherwise noted, all reactions were carried out with a molar ratio of **1**/**2** = 1:10 in 0.5 mL H_2O at 80 °C for 24 h under air. Isolated yield based on **1**.

ring of the α-amino acids could successfully complete the transformation and afforded the corresponding products in 59−76% isolated yields. Then, we changed the methyl of α-keto acids **2a** to ethyl, and reacted with various α-amino acids **1** to get the corresponding products in 54−80% yields. All these reactions were straightforward and obtained fairly good yields. Compared with these results, electron-withdrawing groups on the phenyl ring of the α-amino acids were conducive to the reaction, and the influence of the R^2 group showed no obvious regularity.

A plausible mechanism for the reaction of α-amino acids with α-keto acids is proposed and depicted in Scheme 2. First, a Schiff base **4** (ketimine) was generated from the condensation of amino acid **1a** and keto acid **2a**,[12] then decarboxylation of Schiff base **4** gave another Schiff base **5** (aldimine).[13] **5** underwent aldol type condensation reaction with another molecule of α-keto acid



Scheme 2 Proposed reaction mechanism for the synthesis.

accompanied by the hydrolysis of imine to yield key intermediate **7**.[14] Finally, intramolecular cyclization afforded γ-hydroxybutenolide derivatives **3a**.[15]

According to the proposed mechanism, we considered the possibility that phenylacetaldehyde could be used in replacement of amino acid and conducted the control experiment. Regrettably, the result showed no expected product. To further explore the scope and limitation of the present reaction, several aliphatic α-amino acids **1** like leucine and alanine were used to experience the standard conditions. As a result, the expected products were not obtained. However, when we used methyl pyruvate to react with phenylalanine **1a**, the same product **3a** was obtained in 52% yield.

Conclusion

In summary, we have developed a one-pot synthetic route for the preparation of γ-hydroxybutenolides through catalyst-free annulation of α-amino acids with α-keto acids in water with acceptable yields. One structure of newly resulting γ-hydroxybutenolide was unambiguously confirmed by single crystal X-ray diffraction analysis. The method shows many advantages such as readily available starting materials, mild reaction conditions, operational simplicity, acceptable yields, and requiring no extra catalysts or additions. The entire synthetic route is straightforward and convenient for gram-scale synthesis.

Acknowledgments

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Supplementary Material

Supplementary data associated with this article can be found in the online version, at

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Research highlights

- One-pot catalyst-free synthesis of γ-hydroxybutenolides.
- The method uses water as solvent which is environmentally friendly.
- The product structure was confirmed by single crystal X-ray diffraction analysis.
- The synthetic route is straightforward and convenient for gram-scale synthesis.