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# Annulative coupling of $\alpha$ -substituted acrylic acids and sulfoxonium ylides: easy access to bioactive $\gamma$ -butyrolactones†

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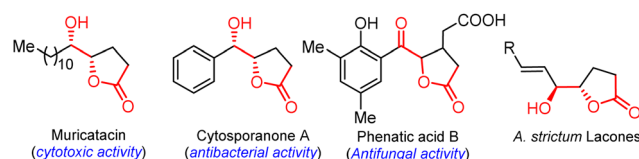
We present a straightforward, catalyst- and additive-free method for synthesizing keto  $\gamma$ -butyrolactones using readily available  $\beta$ -keto sulfoxonium ylides and acrylic acids. This robust approach demonstrates exceptional compatibility with various functional groups on  $\beta$ -keto sulfoxonium ylides and  $\alpha$ -substituted acrylic acids, resulting in good to high yields of the anticipated products. Moreover, the practicality of this approach was validated through large-scale reactions and the successful conversion of some synthesized derivatives into bioactive natural products, including L-factor, muricatacin, and cytosporanone A.

The functionalized  $\gamma$ -butyrolactone structural motif is highly regarded as a privileged structure in medicinal chemistry, found in numerous synthetic compounds and natural products with diverse biological activities (Fig. 1).<sup>1</sup> Due to its array of applications and biological activities, the synthesis of keto  $\gamma$ -butyrolactone has recently garnered significant interest in the literature, following Ochiai's pioneering work.<sup>2</sup> Zhang and co-workers described an alternative approach employing DDQ as the catalyst.<sup>2a</sup> Notably, Ishihara and co-workers significantly advanced the synthesis of keto  $\gamma$ -butyrolactones through their remarkable research work on iodine- and hypervalent iodine-catalyzed lactonization (Scheme 1a).<sup>2b,c</sup> Photoredox-catalyzed photooxidative methods have also been successfully utilized to synthesize keto  $\gamma$ -butyrolactones from a variety of substrates (Scheme 1b).<sup>3</sup> Recently, Zhang, Xu, and co-workers disclosed an elegant approach employing electrocatalytic dehydrogenative esterification of aryl-substituted  $\gamma$ -keto butanoic acids, using *n*-Bu<sub>4</sub>NI as a catalyst, for the synthesis of keto  $\gamma$ -butyrolactones.<sup>4</sup> Despite advancements in synthesizing keto  $\gamma$ -butyrolactones most existing methods are still constrained by expensive reagents, restricted raw material availability, limited substrate scopes and stoichiometric waste. Therefore, it remains highly important to

develop a simple, versatile, and metal-free procedure for access to these scaffolds, which are essential for research in the pharmaceutical industry and academia in their search for bioactive compounds. To our knowledge, the synthesis of keto  $\gamma$ -butyrolactone derivatives from  $\alpha$ -substituted acrylic acids and sulfoxonium ylides has not been previously documented.

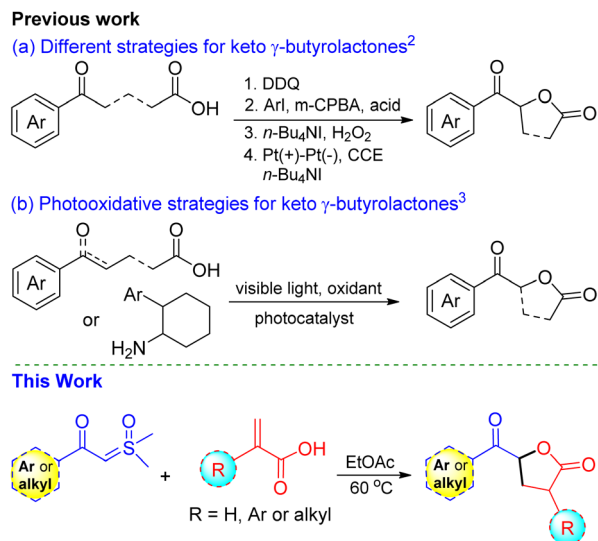
Sulfoxonium ylides have recently gained popularity as diazo surrogates in various chemical reactions owing to their ease of use, bench stability, and extended reactive profiles.<sup>5</sup> They have been widely employed as C1 or C2 synthons in the synthesis of diverse heterocyclic compounds, including furan, pyrrole, pyrimidine, quinolone, and indole, using transition metal catalysts such as Rh, Pd, Ru, Co, and Ir.<sup>6</sup> In our ongoing efforts to develop novel synthetic approaches employing sulfoxonium ylides under metal-free conditions,<sup>7</sup> we present a new method for synthesizing highly functionalized keto  $\gamma$ -butyrolactone derivatives using  $\alpha$ -substituted acrylic acids and sulfoxonium ylides under mild conditions, without any catalysts or additives.

We hypothesized that the acidic proton of acrylic acid could protonate the  $\alpha$ -carbon of sulfoxonium ylides, resulting in the *in situ* formation of a carboxylate ion. This carboxylate ion would then react with the  $\alpha$ -carbon of the ylides to form an  $\alpha$ -oxycarbonyl- $\beta$ -ketone intermediate, releasing DMSO in the process. This intermediate would subsequently undergo tautomerization and intramolecular Michael addition reaction to afford keto  $\gamma$ -butyrolactone. To investigate this hypothesis, we performed experiments at room temperature with the model substrates  $\beta$ -ketosulfoxonium ylide **1a** (0.5 mmol) and acrylic acid **2a** (0.75 mmol) in a toluene (Table 1). Unfortunately, the desired product was not obtained, and the initial substrates


 Fig. 1 Representative natural products with  $\gamma$ -butyrolactone skeleton.

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Scheme 1 Synthetic strategies for keto  $\gamma$ -butyrolactones.

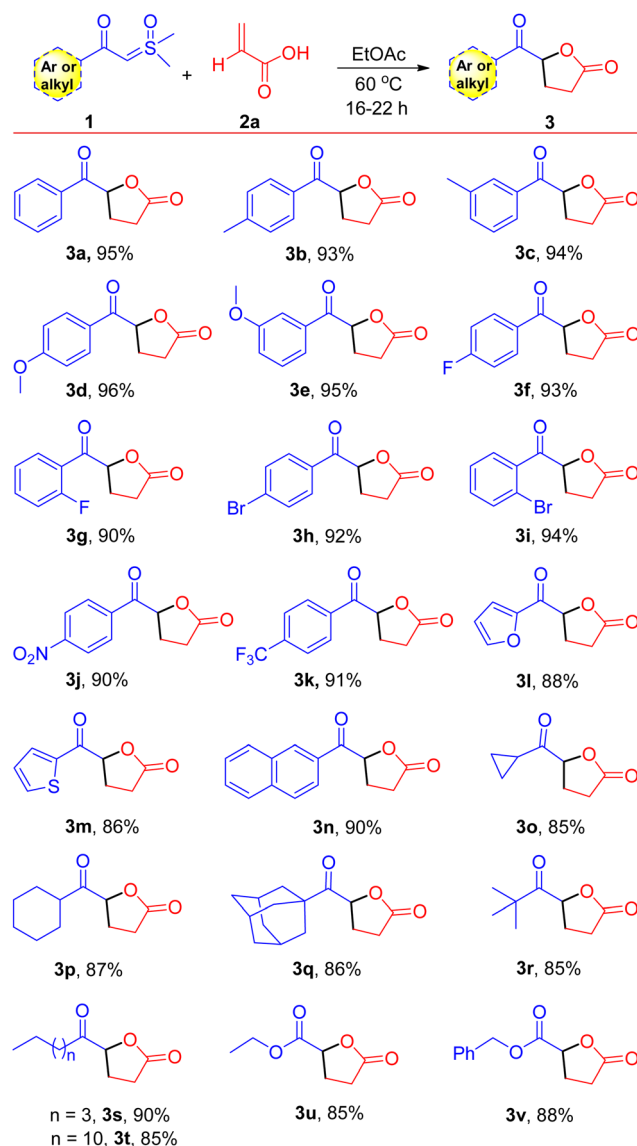
remained unreacted (entry 1). However, we were pleased to observe that increasing the temperature to 60 °C, the model reaction, successfully afforded the anticipated keto  $\gamma$ -butyrolactone **3a** with a 65% yield (entry 2). We further explored a variety of solvents to enhance the reaction conditions and observed that ethyl acetate yielded the best results among aprotic solvents such as CH<sub>3</sub>CN, DCM, CHCl<sub>3</sub>, DMSO, DMF, and DCE (Table 1, entry 9 vs. entries 2–8). We also tested protic solvents such as MeOH, EtOH, and H<sub>2</sub>O, but the results were not promising (entries 13–15). Finally, we established the optimal conditions, resulting in product **3a** with high purity and yield (Table 1, entry 11).

Table 1 Optimization<sup>a</sup>

Entry	Solvent	Time (h)	Temp. (°C)	Yield of <b>3a</b> <sup>b</sup> (%)
1	Toluene	48	rt	nr <sup>c</sup>
2	Toluene	36	60	65
3	CH <sub>3</sub> CN	36	60	45
4	DCM	36	60	25
5	CHCl <sub>3</sub>	36	60	32
6	DMSO	36	60	15
7	DMF	36	60	24
8	DCE	36	60	60
9	EtOAc	30	60	88
10	EtOAc <sup>d</sup>	24	60	90
11	EtOAc <sup>e</sup>	22	60	95
12	EtOAc <sup>f</sup>	22	60	91
13	EtOH	36	60	22
14	MeOH	36	60	35
15	H <sub>2</sub> O	36	60	nr <sup>c</sup>

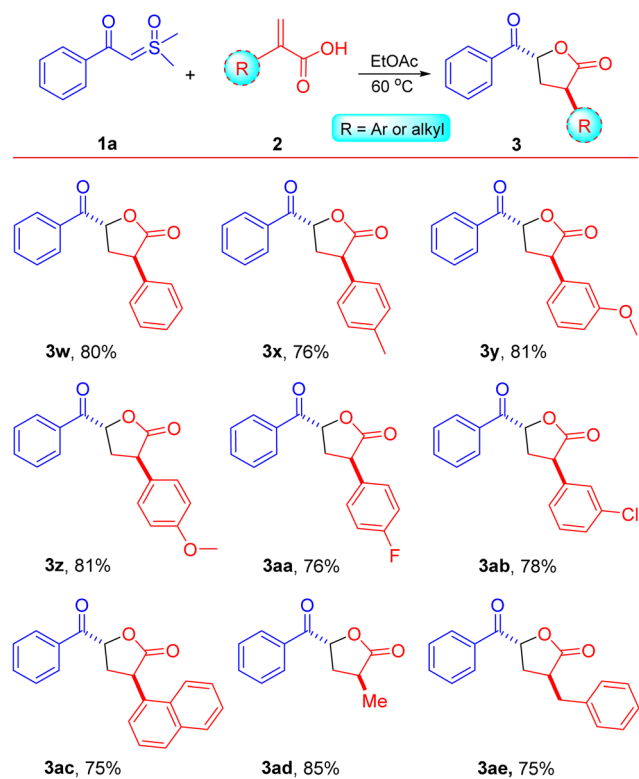
<sup>a</sup> General conditions:  $\beta$ -keto sulfoxonium ylides **1a** (0.50 mmol) and acrylic acids **2a** (0.75 mmol) were mixed in a solvent (1.0 mL) and heated to 60 °C, unless otherwise noted. <sup>b</sup> Isolated yield. <sup>c</sup> No reaction. Acrylic acid **2a**. <sup>d</sup> 1.0 mmol (entry 10). <sup>e</sup> 1.25 mmol (entry 11). <sup>f</sup> 1.50 mmol (entry 12).

The optimized conditions provided a foundation for synthesizing keto  $\gamma$ -butyrolactone derivatives and facilitated their application to various other  $\alpha$ -substituted acrylic acids and aryl/alkyl ylide derivatives. A range of ylides **1** were effectively transformed into their corresponding keto  $\gamma$ -butyrolactones **3**, as shown in Scheme 2 (entries **3a–3t**, 85–96%). Initially, employing acrylic acid **2a**, the effects and generality of aryl/alkyl-containing sulfoxonium ylides **1** were assessed. We observed that  $\beta$ -keto sulfoxonium ylides with electron-donating groups, including methyl and methoxy, at various positions on the aromatic ring, were well accommodated and yielded the anticipated compounds in good yields (entries **3b–3e**, 93–96%). When the aromatic ring of the ylides is decorated with electron-withdrawing substituents, such as bromo, fluoro, trifluoromethyl, and nitro groups at various positions, the reactions proceeded smoothly, yielding the

Scheme 2 Substrate scope. Reaction conditions:  $\beta$ -keto sulfoxonium ylides **1** (0.5 mmol) and acrylic acids **2a** (1.25 mmol) were reacted in EtOAc (1.0 mL) in a sealed tube at 60 °C.

estimated products in high yields (entries **3f–3k**, 90–94%). In addition, some heterocyclic compounds, including thiophene and furan containing sulfoxonium ylides and naphthalene sulfoxonium ylides, were tested with acrylic acid **2a**, resulting in the corresponding keto  $\gamma$ -butyrolactone derivatives in good yields (Scheme 2, entries **3l**, **3m**, and **3n**: 88%, 86%, and 90%, respectively). Moreover, under optimized conditions, some aliphatic  $\beta$ -keto sulfoxonium ylides were assessed, showing good compatibility and resulting in moderate to high yields of their respective products (entries **3o–3t**, 85–90%). Sulfoxonium ylides with other electron-withdrawing groups, such as  $-\text{CO}_2\text{Et}$  and  $-\text{CO}_2\text{Bn}$ , were also well tolerated and resulted in the anticipated products **3u** and **3v**, with yields of 85% and 88%, respectively. To demonstrate the practical applicability of our approach, we conducted a gram-scale reaction employing  $\beta$ -keto sulfoxonium ylide **1a** (1.00 g, 5.10 mmol) and acrylic acid **2a** (0.90 g, 12.75 mmol), which afforded the keto  $\gamma$ -butyrolactone derivative **3a** in 92% yield (0.90 g).

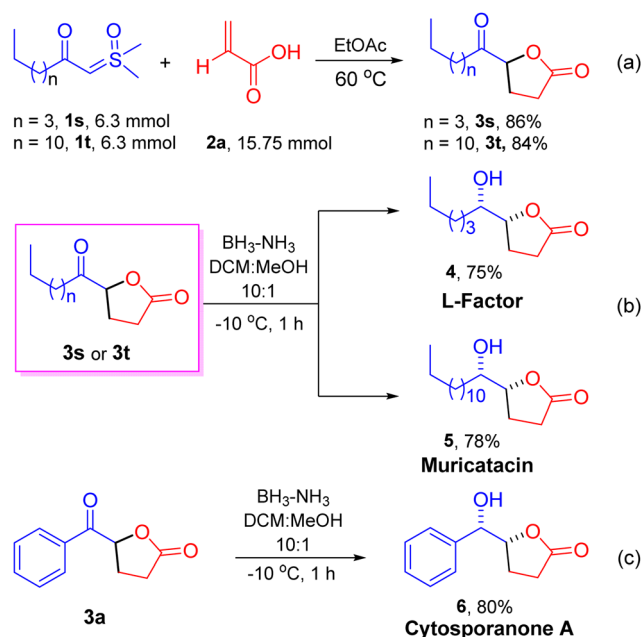
The influence of  $\alpha$ -substituted acrylic acids **2** was then evaluated using sulfoxonium ylide **1a**, as illustrated in Scheme 3. The reactions between sulfoxonium ylide **1a** and various  $\alpha$ -substituted acrylic acids **2** were well-tolerated, resulting in the anticipated products as single diastereomers (>99/1 dr) with anti-configuration in moderate to good yields (entries **3w–3ae**, 75–85%).<sup>8</sup> Both electron-donating and electron-withdrawing groups attached to the  $\alpha$ -position of acrylic acids **2** afforded keto  $\gamma$ -butyrolactone derivatives **3** in good to high yields (entries **3w–3ab**, 76–81%). The reaction of sulfoxonium ylide **1a** with



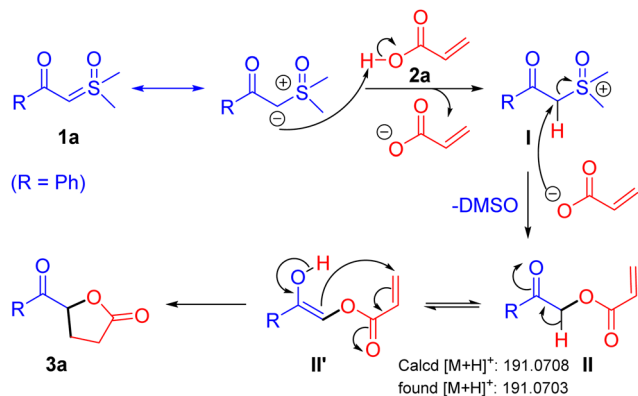
Scheme 3 Substrate scope. Reaction conditions:  $\beta$ -keto sulfoxonium ylide **1a** (0.5 mmol) and acrylic acids **2** (1.25 mmol) were reacted in EtOAc (1.0 mL) in a sealed tube at 60 °C.

naphthyl-substituted acrylic acid **2ac** was found to be highly compatible, yielding the respective compound **3ac** in a 75% yield. Acrylic acids with  $\alpha$ -substitution by alkyl functional groups, such as methyl and benzyl, were also compatible under the optimized conditions and afforded the keto  $\gamma$ -butyrolactone derivatives in good to high yields (85% and 75% for **3ad** and **3ae**, respectively). Substitutions at the  $\beta$ -position of acrylic acid, such as methyl (crotonic acid) and phenyl (cinnamic acid), were incompatible with the existing reaction conditions and failed to afford the anticipated products.

Inspired by the aforementioned methods, we conducted several application experiments to enhance the usefulness and versatility of our developed approach, as illustrated in Scheme 4. Notably, under optimized conditions, we synthesized the keto  $\gamma$ -butyrolactone derivative **3s** on a gram-scale using ylide **1s** (1.20 g, 6.3 mmol) and acrylic acid **2a** (1.08 g, 15.75 mmol) with a yield of 86% (1.00 g) (Scheme 4a). Similarly, the reaction of ylide **1t** (1.8 g, 6.3 mmol) and acrylic acid **2a** (1.08 g, 15.75 mmol) afforded keto  $\gamma$ -butyrolactone derivative **3t** with a 84% (1.5 g) yield. The large-scale synthesis of compounds **3t** and **3s** demonstrates the prospective of the established method, and these derivatives were then used to synthesize a few bioactive natural products. For example, diastereoselective reduction of keto  $\gamma$ -butyrolactone derivative **3s** with  $\text{BH}_3 \cdot \text{NH}_3$  complex afforded the natural products L-factor<sup>9</sup> **4** and muricatacin<sup>10</sup> **5** with >99/1 dr in 75% and 78% yields, respectively (Scheme 4b). Muricatacin, an acetogenin extracted from the seeds of the tropical fruit *Annona muricata* L., has been identified as a quasi-racemic compound (*ca.* 25% ee).<sup>1g</sup> It has shown cytotoxic effects on human tumor cell lines and served as a precursor for synthesizing higher acetogenin natural products.<sup>11</sup> Additionally, the diastereoselective reduction of keto  $\gamma$ -butyrolactone derivative **3a** furnished the natural product cytosporanone A **6**<sup>1b,d</sup> (>99/1 dr)<sup>4</sup> with 80% yield (Scheme 4c).



Scheme 4 Synthetic applications.



Scheme 5 Plausible reaction mechanism.

Following a notable demonstration of the practical synthesis of keto  $\gamma$ -butyrolactone derivatives from sulfoxonium ylides and  $\alpha$ -substituted acrylic acids, a probable reaction mechanism is illustrated in Scheme 5. Initially, the  $\alpha$ -carbon of  $\beta$ -keto sulfoxonium ylide **1a** engages with the acidic proton of the acrylic acid, forming intermediate **I**. Subsequently, a nucleophilic attack at the  $\alpha$ -carbon position of intermediate **I** by the *in situ* generated carboxylate ion produces  $\alpha$ -acyloxy ketone intermediate **II**,<sup>12</sup> releasing DMSO. Finally, the  $\alpha$ -acyloxy ketone intermediate **II** tautomerizes to **II'**, which undergoes intramolecular cyclization *via* a Michael addition reaction, resulting in the formation of the keto  $\gamma$ -butyrolactone derivative **3a**.

In conclusion, we have established a robust, catalyst- and additive-free synthetic strategy for the synthesis of keto  $\gamma$ -butyrolactones from  $\alpha$ -substituted acrylic acids and  $\beta$ -keto sulfoxonium ylides. These  $\beta$ -keto sulfoxonium ylides and  $\alpha$ -substituted acrylic acids, featuring various functional groups, showed exceptional compatibility, yielding the desired products with good yields. The practicality of this strategy was further validated through a large-scale reaction, the synthesis of numerous keto  $\gamma$ -butyrolactone derivatives, and their conversion into some bioactive molecules such as L-factor, muricatacin, and cytosporanone A.

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## Data availability

The data supporting this article have been included as part of the ESI.†

## Conflicts of interest

There are no conflicts to declare.

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