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Base-catalyzed bis-sulfenylation of γ-substituted butenolides for the synthesis of α,α-bisthiofunctionalized butenolide derivatives

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ABSTRACT

A method for the synthesis of α,α-bisthiofunctionalized butenolide compounds has been successfully developed. The bis-sulfenylation of γ-substituted butenolides at α-position is promoted by using triethylamine as the catalyst and *N*-(aryl(alkyl)sulfanyl)succinimides or *N*-(phenylsulfanyl)phthalimides as sulfenylating reagents under mild reaction conditions. A range of α-sulfenylated butenolide derivatives could be smoothly obtained in moderate to excellent yields. A preliminary attempt at the catalytic asymmetric α-sulfenylation of α-methyl-γ-phenyl-substituted butenolide was also conducted and afforded promising enantioselectivity.

1. Introduction

Sulfur-containing organic compounds have wide applications in pharmaceutical and agrochemical chemistry, sulfur-containing polymers and materials science.[1] The preparation of sulfur-containing compounds has attracted the continual attention of chemists. Particularly, the synthesis of sulfur-containing compounds via direct C–S bond-forming has deserved special interest over the past few decades.[2] A variety of approaches for the C–S bond-forming have been achieved, especially such as the addition and substitution reactions by using various sulfur nucleophiles.[2–4] Even so, taking into account the potential applications of sulfur-containing compounds in various areas, the development of more effective approaches for the preparation of them is still highly desirable.

In the all sorts of sulfur electrophiles,[5] *N*-sulfanylsuccinimides and *N*-sulfanylphthalimides belong to a type of commonly used sulfenylating reagents for the C–S bond-forming. They often serving as sulfur sources react with various nucleophiles for the synthesis of sulfur-containing compounds.[6,7] On the other hand, γ-substituted butenolides playing as nucleophiles could be functionalized at the γ-position by using different electrophiles, leading to diverse γ,γ-disubstituted butenolide skeletons,[8] which are a sort of the most prevalent structural moieties in biologically active natural products and pharmaceutically relevant molecules.[9] However, we noticed that there is no any report on the reaction of γ-substituted butenolides and *N*-sulfanylsuccinimides or *N*-sulfanylphthalimides so far, although the reaction is able to furnish a new type of sulfur-containing butenolide compounds.

Based on our own researches on the reaction of γ-substituted butenolides with various electrophiles[10] and the relevant reports in literatures,[8] we envisioned that γ-substituted butenolide **1** could react with *N*-(phenylsulfanyl)succinimide **2** under base condition, forming the expected γ-sulfenylated butenolide product **3'** (Scheme 1(a)). However, in our preliminary studies, we actually obtained the α,α-bisthiofunctionalized butenolide **3** rather than γ-sulfenylated butenolide **3′** from the reaction (Scheme 1(b)). In the light of this preliminary result, we presumed that the α-monosulfenylated product **3″** or α,γ-disulfenylated product **3‴** should be observed in the reaction mixture (Scheme 1(c)). In fact, we discovered that there were no products **3″** and **3‴** at all in the

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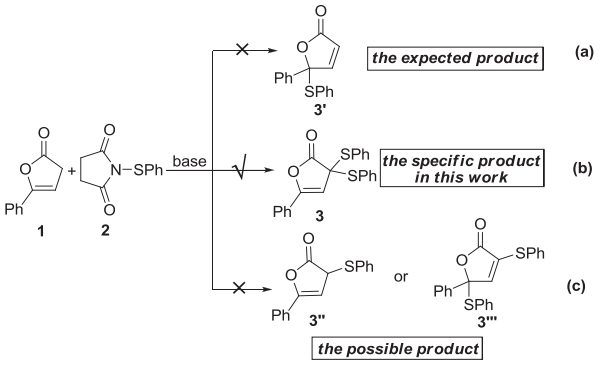


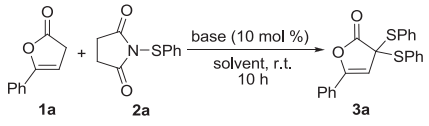
Scheme 1. Reaction of γ-substituted butenolide reacting with *N*-(phenylsulfanyl)succinimide affords the exclusive α,α-bisthiofunctionalized butenolide product.

reaction system, but only α,α-bisthiofunctionalized butenolide **3** was obtained. These results suggested that the sulfenylation reaction with *N*-sulfanylsuccinimide preferentially occurs at the α-position rather than at the γ-position of the γ-substituted butenolide **1**. Nevertheless, we also conclude that, after the mono-sulfenylation at the α-position of the γ-substituted butenolide, the corresponding mono-sulfenylation intermediate **3**″ will be more inclined to be sulfenylated again at the α-position. Therefore, the reaction exclusively provides the α,α-bisthiofunctionalized butenolide product **3** (Scheme 1(b)). Herein, we hope to report our research results on this subject. Notably, this work will represent the first example about the α,α-bis-sulfenylation of γ-substituted butenolide compounds.

2. Results and discussion

Initially, the reaction of γ-phenyl-substituted butenolide **1a** with *N*-(phenylsulfanyl)succinimide **2a** was carried out as a model reaction to screen a set of optimal reaction conditions. As illustrated in Table 1, the reaction proceeded smoothly in CH_2Cl_2 with addition of 10 mol % of Na_2CO_3 as the catalyst at room temperature, giving α,α-bisthiofunctionalized butenolide product **3a** in 62% yield

Table 1
Optimization of the reaction conditions.[a]



Entry	Solvent	Base	Yield (%)[b]
1	CH_2Cl_2	Na_2CO_3	62
2	CH_2Cl_2	K_2CO_3	90
3	CH_2Cl_2	DBU	80
4	CH_2Cl_2	DMAP	63
5	CH_2Cl_2	DABCO	90
6	CH_2Cl_2	Et_3N	98
7	THF	Et_3N	47
8	CH_3CN	Et_3N	92
9	toluene	Et_3N	41
10	EtOAc	Et_3N	65

[a] The reactions were carried out with γ-phenyl-substituted butenolide **1a** (0.20 mmol), *N*-(phenylsulfanyl)succinimide **2a** (0.41 mmol), and base (0.02 mmol) in 2.0 mL of solvent at room temperature for 10 h. DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene, DMAP = 4-dimethylaminopyridine, DABCO = 1,4-diazabicyclo[2.2.2]octane.

[b] Isolated yields.

(Table 1, entry 1). And then, replacing the Na_2CO_3 with K_2CO_3, the reaction could give **3a** in a higher yield up to 90% (Table 1, entry 2). Using some other organic bases, such as DBU, DMAP, DABCO and triethylamine as catalysts (Table 1, entries 3–6), the reaction also worked well and high to 98% yield could be obtained with triethylamine (Table 1, entry 6). Ultimately, we undertook a screen of solvents with 10 mol % triethylamine at room temperature (Table 1, entries 7–10). In all the solvents evaluated, product **3a** could be obtained in moderate to excellent yield, but by comparison, the use of CH_2Cl_2 as solvent afforded the optimal result (Table 1, entry 6). Notably, if only using 1.0 equivalent of **2a** for the reaction, it was also observed that only α,α-bisthiofunctionalized butenolide **3a** could be obtained with low yield. Based on the above investigations, the application of 10 mol % triethylamine as catalyst in CH_2Cl_2 at room temperature and at the ratio of substrates **1a**:**2a** = 1.0:2.05 was identified as the optimal reaction condition.

With the optimal reaction conditions in hand, the scope of the bis-sulfenylation of γ-substituted butenolides with respect to both nucleophilic butenolides and electrophilic sulfenylation reagents was investigated (Table 2). Firstly, various γ-substituted butenolide substrates were examined by reacting with *N*-(phenylsulfanyl) succinimide **2a**. It was found that different butenolides **1b-e** bearing electron-rich or electron-deficient γ-aryl group all reacted efficiently with **2a** and afforded the respective α,α-bissulfenylated products in high to excellent yields (88–98%, Table 2, entries 1–4). Moreover, the naphthyl moiety was also tolerated in the bis-sulfenylation process, delivering product **3f** in 88% yield (Table 2, entry 5). Nevertheless, the reaction also could be conducted with γ-alkyl butenolide **1g**, the desired product **3g** was obtained only in 43% yield even with 72 h (Table 2, entry 6). On the other hand, the variation of electrophilic sulfenylation reagents was also tested by reacting with γ-phenyl-substituted butenolide **1a**. For *N*-(arylsulfanyl)succinimides **2b-e** bearing electron-donating groups, regardless of the position of the substituent on the phenyl rings, the reactions furnished the corresponding products **3h-k** in 78–88% yields (Table 2, entries 7–10). Additionally, the similar results also could be observed for the electron-withdrawing groups incorporating to *N*-(arylsulfanyl)succinimide substrates **2f-h**, providing products **3l-n** in excellent results (Table 2, entries 11–13). Notably, the possibility to employ *N*-(alkylsulfanyl)succinimides **2i-j** as the electrophilic sulfenylation reagents was also evaluated. The reactions afforded the corresponding α,α-bisthiofunctionalized butenolides **3o** and **3p** in 55% and 67% yields, respectively (Table 2, entries 14 and 15). Ultimately, we also tried to use *N*-(phenylsulfanyl)phthalimide **2k** as sulfenylation reagent by reacting with **1a**, the reaction could smoothly provide the desired product **3a** in 85% yield (Table 2, entry 16). Unfortunately, in the reaction between **1g** and **2k**, the product **3g** could be obtained only in 21% yield despite with prolonged reaction time to 72 h (Table 2, entry 17).

In addition to the spectroscopic data (^1H, ^{13}C NMR, and mass spectroscopy analysis), the X-ray crystallography of the product **3a** was achieved (Fig. 1), which unambiguously confirmed the structures of the obtained α,α-bisthiofunctionalized butenolide compounds.[11]

Encouraged by the above promising results, we next turned our attention to the investigation on the possibility of the α-sulfenylation of α-monosubstituted butenolide. To our delight, the attempts to perform the reactions using α-methyl-γ-phenyl-substituted butenolide **4** with different electrophilic sulfenylation reagents revealed the feasibility of the catalyst system described herein (Scheme 2). Under the standard reaction conditions, the reaction of α-methyl-γ-phenyl-substituted butenolide **4** with *N*-(phenylsulfanyl)succinimide **2a** occurred well and gave the desired α-sulfenylation product **5a** in 98% yield.[12] Nevertheless, we also found that both the *N*-(arylsulfanyl)succinimide **2d** bearing an