Tetrahedron Letters 51 (2010) 6918–6920

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Efficient synthesis of highly functionalized vinylogous thiol esters

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ARTICLE INFO

Article history:
Received 28 August 2010
Revised 21 October 2010
Accepted 26 October 2010
Available online 30 October 2010

Keywords:
Vinylogous thiol esters
α-Alkenoylketene diethylthioacetals
Diethyl malonate
Retro-Michael addition
Michael addition

ABSTRACT

A series of vinylogous thiol esters **2**, **3** and 2,6-dioxo-1,2,5,6-tetrahydropyridines (cyclic vinylogous thiol esters) **4** were prepared in high to excellent yields from the tandem reaction of readily available α-alkenoylketene diethylthioacetals **1** and diethyl malonate. A plausible mechanism, which involves a base catalyzed retro-Michael ring opening of cyclohexanenes **2** to give vinylogous thiol ester **3**, is disclosed.

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As versatile intermediates, functionalized ketene dithioacetals and their analogues have found wide applications in organic synthesis.[1,2] During the course of our studies, we found that the readily available highly functionalized α-alkenoylketene diethylthioacetals **1** and α-alkenoylketene cyclic dithioacetals **1′** can serve as useful building blocks in the synthesis of various carbo- and heterocyclic compounds (Fig. 1).[2g,3–9] For example, the reactions of five-carbon 1,5-dielectrophilic α-alkenoylketene diethylthioacetals **1** with carbon,[2g,6] nitrogen,[7] sulfur,[8] and selenium nucleophiles[9] can afford the corresponding six-membered ring compounds via [5+1] annulation. In this communication, the efficient synthesis of highly functionalized vinylogous thiol esters **2**, **3** and 2,6-dioxo-1,2,5,6-tetrahydropyridines (cyclic vinylogous thiol esters) **4** from **1** is described (Fig. 1). In addition, a new strategy, which involves a base catalyzed retro-Michael ring opening of cyclohexanones **2** to give vinylogous thiol ester **3**, is disclosed.

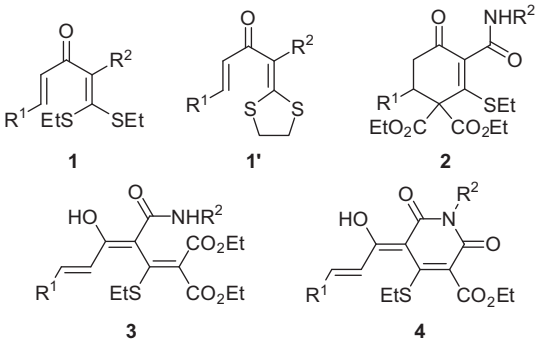
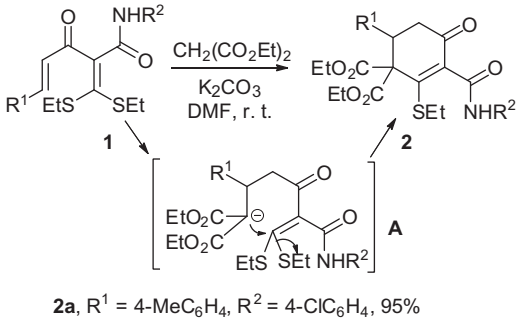


Figure 1. α-Alkenoylketene thioacetals **1**, **1′** and vinylogous thiol esters **2**, **3** and 2,6-dioxo-1,2,5,6-tetrahydropyridines **4**.

In the present research, the reactions of α-alkenoylketene diethylthioacetals **1** with diethyl malonate under basic conditions were investigated. As a result, the desired products, cyclic vinylogous thiol esters **2a–c**, could be obtained in excellent yields from the reactions of **1a–c** (2.0 mmol) with diethyl malonate (2.2 mmol) in DMF (10 mL) in the presence of K_2CO_3 (4.0 mmol) at ambient temperature for 4 h via the [5C+1C] annulation process, involving a tandem Michael addition followed by an intramolecular Michael addition and elimination of ethylthiol (Scheme 1).[6,2g]



2a, R^1 = 4-MeC_6H_4, R^2 = 4-ClC_6H_4, 95%
2b, R^1 = 4-$MeOC_6H_4$, R^2 = Ph, 85%
2c, R^1 = 4-$MeOC_6H_4$, R^2 = 2,4-$Me_2C_6H_3$, 81%

Scheme 1. Synthesis of cyclic vinylogous thiol esters **2**.

Interestingly, it was found that the highly functionalized vinylogous thiol ester **3a** could be produced in 90% isolated yield simply by stirring the reaction mixture of **1a** (2.0 mmol) and diethyl

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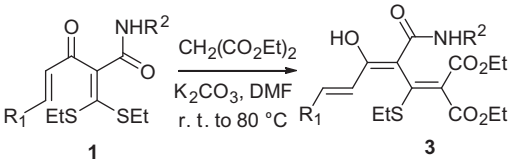
malonate (2.2 mmol) in DMF (10 mL) in the presence of K_2CO_3 (4.0 mmol) first at room temperature for 4 h to complete consumption of **1a** (monitored by TLC) and then at about 80 °C for additional 1 h (Table 1, entry 1). In another case, vinylogous thiol ester **3a** was obtained in 92% yield from the ring-opening of cyclohexanone **2a** (1.0 mmol) catalyzed by K_2CO_3 (5 mol %) in DMF (5 mL) at 80 °C for 1 h. The above results indicate that the reaction of **1** with diethyl malonate could be controlled to exclusively yield **2** or **3** by varying the reaction temperature. The above reaction proceeded in a chemo- and stereoselective manner. The structure of vinylogous thiol ester **3a**, which contains an highly functionalized conjugated triene units, was established by the X-ray single crystal analysis (Fig. 2)[10] and the ^{1}H NMR and ^{13}C NMR spectra (for details, please see Supplementary data).

Dieter et al. have reported the chemo- and stereoselective synthesis of vinylogous thiol esters through the reactions of organocuprates with α-oxoketene dithioacetals via a conjugate addition–alkylthio elimination pathway.[11a] Other methods for the preparation of vinylogous thiol esters involved transition-metal-catalyzed acetylthiolation of alkynes,[11b] reaction of cyclic vinylogous esters with thiols,[11c] and the radical reaction of aromatic disulfides, alkynes, and isonitriles under photolytic conditions.[11d] Therefore, the transformation of α-alkenoylketene diethylthioacetal **1a** into vinylogous thiol ester **3a** represents a new efficient access to highly functionalized vinylogous thiol esters starting from

Table 1
One-pot Synthesis of highly functionalized vinylogous thiol esters **3**



Entry	1	R^1	R^2	Time[a] (h)	3	Yield (%)
1	**a**	4-MePh	4-ClPh	4.0	**a**	90
2	**b**	4-MeOPh	4-ClPh	4.5	**b**	87
3	**c**	3,4-O_2CH_2Ph	4-ClPh	3.5	**c**	92
4	**d**	Ph	4-ClPh	4.0	**d**	81
5	**e**	4-ClPh	4-ClPh	4.0	**e**	86
6	**f**	2-thienyl	4-ClPh	6.0	**f**	70
7	**g**	3-pyridyl	4-ClPh	10.0	**g**	76
8	**h**	PhCH=CH	4-ClPh	12.0	**h**	65
9	**i**	4-MePh	2-MeOPh	4.0	**i**	76
10	**j**	4-MePh	Ph	4.0	**j**	80
11	**k**	4-MePh	2,4-Me_2Ph	4.0	**k**	78
12	**l**	4-MePh	2-MePh	4.0	**l**	78

[a] Time for room temperature.

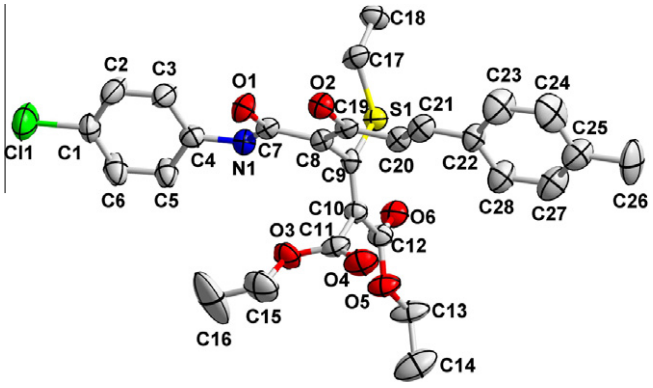
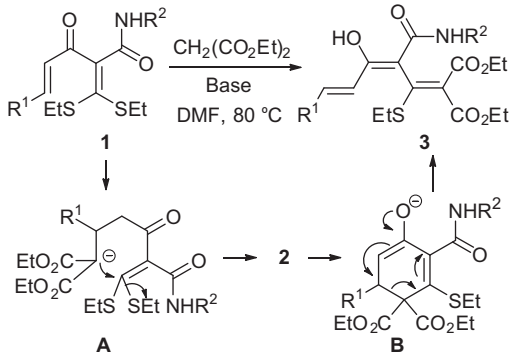
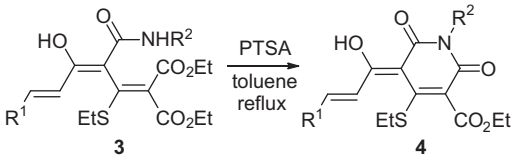


Figure 2. ORTEP drawing of **3a**.



Scheme 2. Proposed mechanism for the formation of **3**.

Table 2
Synthesis of 2,6-dioxo-1,2,5,6-tetrahydropyridines **4**



Entry	3	R^1	R^2	4	Yield (%)
1	**a**	4-MePh	4-ClPh	**a**	91
2	**b**	4-MeOPh	4-ClPh	**b**	86
3	**c**	3,4-O_2CH_2Ph	4-ClPh	**c**	88
4	**d**	Ph	4-ClPh	**d**	81
5	**e**	4-ClPh	4-ClPh	**e**	83
6	**j**	4-MeOPh	Ph	**f**	90

the easily available substrates. Under identical conditions as shown in Table 1, entry 1, a series of vinylogous thiol esters **3** were synthesized and the results are showed in Table 1. The results in Table 1 clearly indicate the scope and generality of the reaction with respect to various R^1 groups of substrate **1**, including aromatic rings with electron-donating (entries 1–3) or electro-withdrawing group (entry 5), heteroaromatic (entries 6 and 7), and aliphatic group (entry 8). In addition, the R^2 group (substituted phenyl) shows little effect on the yields of vinylogous thiol esters **3** (entries 9–12).

Based on above results, the one-pot synthesis of vinylogous thiol esters **3** could involve a retro-Michael ring opening of cyclic vinylogous thiol esters **2**. Thus, the mechanism of formation of vinylogous thiol esters **3** involves three steps: an intermolecular Michael reaction, an intramolecular reaction, and finally a retro-Michael reaction (Scheme 2).[12] To our knowledge, this transformation is the first example of base induced ring opening of cyclohexenone derivatives, although the corresponding retro-oxa Michael ring opening of chromones has been well established.[13]

With the easily available vinylogous thiol esters **3** at hand, our attention was then turned to the intramolecular cyclization to prepare the 2,6-dioxo-1,2,5,6-tetrahydropyridines **4** (Table 2). It was found that no reaction occurred when **3a** was treated in toluene for 6 h at reflux. Whereas in the presence of catalytic amount of *p*-toluenesulfonic acid (PTSA, 10 mol %), product **4a** was obtained in 91% yield by the reaction of **3a** (1.0 mmol) in toluene (5 mL) for 4 h at reflux (Table 2, entry 1). Under above conditions, 2,6-dioxo-1,2,5,6-tetrahydropyridines **4b–f** were prepared in high yields (Table 2, entries 2–6).

In conclusion, we have developed a convenient synthesis of a series of highly functionalized vinylogous thiol esters **2**, **3** and 2,6-dioxo-1,2,5,6-tetrahydropyridines **4** from the easily available

α-alkenoylketene diethylthioacetals **1** and diethyl malonate. The one-pot synthesis of highly functionalized vinylogous thiol esters **3** involves a novel mechanism of base induced ring opening of cyclohexenone derivatives **2**. The simplicity of execution, high yields, and promising synthetic applications of the products make the protocol very attractive.[14,15] Further studies are in progress.

Acknowledgments

Financial supports of this research provided by the NNSFC (20872015), the Science Foundation for Young Teachers of NENU (20090404), the Young Scientific Research Foundation of Jilin Province (20090149) and China Postdoctoral Science Foundation (20080431049) are greatly acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.129.

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