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A tandem reaction of 2-acetylmethylene-1,3-dithiolanes via fragmentation of the dithiolane ring in the presence of amines: a facile route to functionalized thioamides

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Abstract—A facile and efficient route to functionalized thioamides has been developed by a tandem reaction of 2-acetylmethylene-1,3-dithiolanes via fragmentation of the dithiolane ring upon heating and in the presence of an amine.

Thioamides are essential building blocks in the preparation of a large number of heterocycles.[1] Recently, considerable interest has been paid on the functionalization of thioamides and their use in organic synthesis, including regio- and stereoselective heterocyclization reactions.[2] In particular, this concerns the thioamides having another reactive site in the molecule, which may serve as more useful building blocks. In view of their synthetic importance, several routes have been developed to gain access to thioamides and functionalized thioamides from various substrates.[3] Among them, the thionation[4a] of the corresponding amides with the aid of phosphorus pentasulfide[4b,c] or Lawesson's reagent[4d,e] has demonstrated good general use. However, these methods usually need excess of thionation reagents, lengthy reaction time and dry hydrocarbon solvent, and usually result in the generation of side products. Hence, new methods towards thioamides, especially functionalized thioamides, are still required.

Over the past few decades, α-oxo ketene (*S*,*S*)-acetals have been emerging as versatile intermediates in organic synthesis.[5] During our studies, we found that the alkylthio group has significant influence on the reaction manner and reactivity of ketene (*S*,*S*)-acetals.[6] As shown in Figure 1, a C_{sp^2}–S bond cleavage (type A, i.e., the alkylthio group acts as a leaving group) is frequently involved

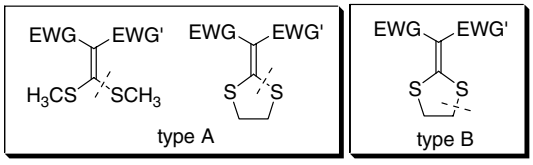

Figure 1.

in the reactions of ketene (*S*,*S*)-acetals. Regarding this point, the [5C + 1C, (1N), (1S)] annulation strategies based on alkenoyl ketene (*S*,*S*)-acetals as the 1,5-bielectrophilic five-carbon synthons have been developed and highly substituted phenolic rings,[6a] pyridones,[6b] pyrido[2,3-*d*]pyrimidines[6c] and thioptran-4-ones[6d] were constructed. We also developed ketene (*S*,*S*)-acetal compounds as odourless and practical thiol equivalents used in thioacetalization[6e] or thio-Michael addition reactions.[6f] However, examples corresponding to the C_{sp^3}–S bond cleavage of 1,3-dithiolane in ketene (*S*,*S*)-acetals (type B, Fig. 1) are rare.[7] Asokan et al. described a demethylation and fragmentation reactions of the corresponding α-oxoketene dithioacetals in the presence of a strong base, such as NaH.[8] In order to explore this unusual type of C–S bond cleavage and the synthetic potential, much attention has been paid in our group. Recently, in our research for the synthesis of multisubstituted thiophenes, the fragmentation of 1,3-dithiolanes in the form of C_{sp^3}–S bond cleavage in 2-alkenoylmethylene-1,3-dithiolanes was found to take place in the presence of an amine.[6g] As a continuing research, we wish to present here a facile preparation

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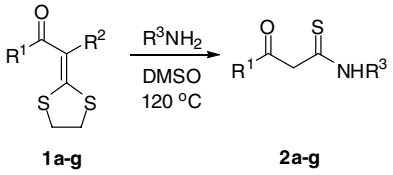
of functionalized thioamides, namely α-carbonyl thioamides, by a tandem reaction of 2-acetylmethylene-1,3-dithiolanes via fragmentation of the dithiolane ring in the presence of an amine. This protocol provided an efficient entry to a wide range of functionalized thioamides from easily available ketene (*S*,*S*)-acetals.[6h]

Initially, the reaction of ethyl 2-(1,3-dithiolan-2-ylidene)-3-oxobutanoate **1a** and *n*-butylamine was examined to optimize the reaction conditions, including the variation of the reaction temperatures (room temperature to 120 °C), solvents (CH_3CN, THF, DMF and DMSO) and the feed ratio of **1a** to amine (Scheme 1). At room temperature, the reaction of **1a** (1.0 mmol) with *n*-butylamine (1.2 mmol) in CH_3CN could not occur at all. However, at reflux temperature, the reaction gave the only product, α-ethoxycarbonyl thioamide **2aa**, in 15% yield and its structure was characterized on the basis of the spectral and analytical data. It was found in our experiment that DMSO was the most efficient solvent. In this case, the reaction of **1a** (1.0 mmol) with *n*-butylamine (1.2 mmol) afforded the desired product **2aa** in 87% yield upon heating to 120 °C for 1.5 h (Table 1, entry 1).

Next, with the aim to explore the scope of the reaction mentioned above (Scheme 1), a variety of amines were selected to react with **1a** under the optimized reaction conditions.[9] The experimental results indicate that aliphatic amines are efficient for the reaction. For example, the reactions of **1a** with methylamine, ethylamine and benzylamine proceeded smoothly and the desired thioamides **2ab**–**e** were obtained in good to high yields (Table 1, entries 2–4). Particularly, when chiral (−)-benzylmethylamine was used, product **2ae** could be achieved without any difficulty (Table 1, entry 5). Whereas, it was found that secondary, tertiary and aromatic amines (such as diethylamine, triethylamine and aniline) were inefficient for the above reaction. In addition, the dinucleophiles, such as 1,2-ethyldiamine, 1,3-propyldiamine and ethanolamine, were also subjected to the reaction sequences. However, the products were not thioamides, but the corresponding cyclic *N*,*N*- or *N*,*O*-acetals, which are in agreement with our previous results.[10]



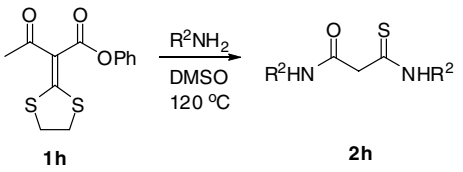
Scheme 1. Synthesis of functionalized thioamides **2a**–**g**.

To further extend this interesting reaction, a series of ketene-(*S*,*S*)-acetal substrates **1b**–**h** were synthesized from the corresponding β-ketoesters, benzoylacetones, and β-ketoamides, respectively.[6] Then, the reactions of **1b**–**g** (1.0 mmol) with selected primary amines like *n*-butylamine, benzylamine or ethylamine (1.2 mmol) were carried out under the identical conditions described above (Table 1). As a result, substrates **1b**–**g** proved to be successful and the desired functionalized thioamides **2b**–**g** were produced in good to high yields (Table 1, entries 6–15). The NMR spectra confirmed the presence of a mixture of an enol and keto tautomers for **2b**, **2d** and **2f** in $CDCl_3$. It was noteworthy that when phenyl 2-(1,3-dithiolan-2-ylidene)-3-oxobutanoate (**1h**) was reacted with the aliphatic primary amines, the aminolysis of the phenolic ester was observed (Scheme 2). With the variation of the amines (2.5 equiv), a series of thiomalonamides **2ha**–**d** were obtained in high yields (Table 1, entries 16–19). Indeed, this protocol provides

Table 1. Reactions of EWG-containing 2-methylene-1,3-dithiolanes with amines

Entry	Substrate **1**	R^1	R^2	R^3	Time (h)	Product **2**	Yield[a] (%)
1	**1a**	OEt	COMe	*n*-Bu	1.5	**2aa**	87
2	**1a**	OEt	COMe	Me	0.7	**2ab**	81
3	**1a**	OEt	COMe	Et	1.5	**2ac**	76
4	**1a**	OEt	COMe	Bn	1.7	**2ad**	70
5	**1a**	OEt	COMe	(−)-PhCH(CH_3)	2.0	**2ae**	62
6	**1b**	Me	COMe	*n*-Bu	1.0	**2ba**	82
7	**1b**	Me	COMe	Bn	1.1	**2bb**	84 (5:1)[b]
8	**1c**	OMe	COMe	*n*-Bu	1.2	**2c**	80
9	**1d**	Ph	COMe	*n*-Bu	1.0	**2da**	81 (5:1)[b]
10	**1d**	Ph	COMe	Bn	1.5	**2db**	82 (3:1)
11	**1e**	*p*-EtOPh	COMe	*n*-Bu	2.5	**2ea**	88
12	**1e**	*p*-EtOPh	COMe	Bn	2.0	**2eb**	90
13	**1f**	*p*-ClPh	COMe	*n*-Bu	1.5	**2fa**	84 (2:1)[b]
14	**1f**	*p*-ClPh	COMe	Bn	2.5	**2fb**	82 (2:1)[b]
15	**1g**	NHPh	COMe	Et	2.0	**2g**	78
16	**1h**	OPh	COMe	*n*-Bu	0.8	**2ha**	85
17	**1h**	OPh	COMe	Me	0.9	**2hb**	82
18	**1h**	OPh	COMe	Et	0.8	**2hc**	80
19	**1h**	OPh	COMe	Bn	0.9	**2hd**	74
20	**1i**	Me	H	*n*-Bu	8	—	—
21	**1j**	Ph	H	*n*-Bu	8	—	—
22	**1k**	OEt	COEt	*n*-Bu	8	—	—

[a] Isolated yields over silica gel chromatography.
[b] The ratio of keto to enol estimated via ^1H NMR spectra.

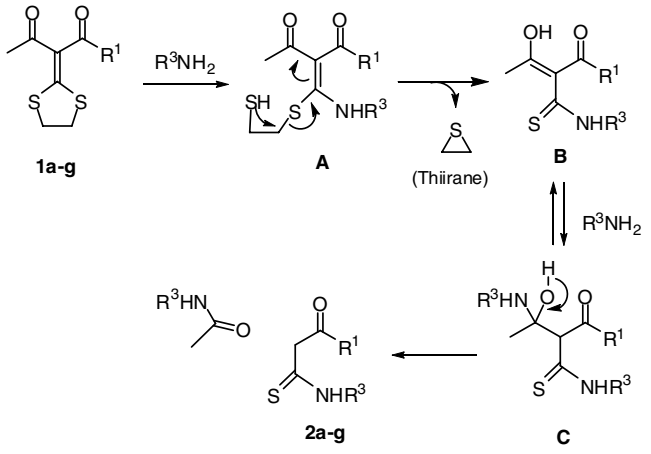


Scheme 2. Synthesis of thiomalonamides **2h**.

a new and convenient route towards various functionalized thioamides of type **2.** It should be noted that the substrates with only one electron-withdrawing acetyl or benzoyl group (**1i** and **1j**) could not undergo the fragmentation reaction explored here, same as the substrates without any acetyl groups (**1k**). In these cases, the substrates were recovered quantitatively (Table 1, entries 20–22). In addition, the fragmentation reaction of six-membered 2-acetylmethylene 1,3-dithiane with primary amine under identical conditions was not observed.

On the basis of the experimental results, a plausible mechanism for the formation of thioamides **2** is proposed, as depicted in Scheme 3. Initially, a S_NV (nucleophilic vinylic substitution) type reaction[11,12] leads to the fragmentation of 1,3-dithiolane, giving rise to the formation of the intermediate A. Driven by two strong electron-withdrawing groups, an intramolecular elimination of thiirane takes place and intermediate B is formed.[13] Finally, thioamides **2** were produced through a regioselective deacetylation (B→C→**2**).[14] Such a type of deacetylation is similar to that reported by Avery and co-workers.[14a]

In conclusion, in the presence of aliphatic primary amines and upon heating, the ring fragmentation of 2-acetylmethylene-1,3-dithiolanes and subsequent transformation into functionalized thioamides were developed. In this reaction, not only the special C–S bond cleavage manner involved is attractive, but the reaction also offers an effective entry to a range of useful functionalized thioamides in a one-pot, catalyst-free and high-yielding procedure. At the end, this reaction represents one of the few examples towards the synthesis of thioamides without the utilization of phosphorus pentasulfide or Lawesson's reagent.



Scheme 3. Proposed mechanism for the formation of thioamides **2a**–**g**.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.09.065.

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