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Dithioester-enabled chemodivergent synthesis of acids, amides and isothiazoles via C—C bond cleavage and C—O/C—N/C—S bond formations under metal- and catalyst-free conditions

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ABSTRACT

An operationally simple and user-friendly process to access privileged scaffolds such as acids, amides and isothiazoles has been devised employing β-ketodithioesters for the first time. Remarkably, the new protocol involves combination of C—C bond cleavage and C—O/C—N/N—S bond formations in one-pot. Aqueous ammonia led to the formation of skeletally distinct amide and isothiazole, whereas aqueous NaOH enabled the formation of aromatic acid near quantitative yield. This practical approach, which can dramatically streamline the synthesis of simple molecules, is highly chemoselective, cost-effective, amenable to gram scale, insensitive to moisture as well as bears high functional group compatibility.

The cleavage and formation of carbon-carbon and carbon-heteroatom bonds are of fundamental importance in organic synthesis, and lies at the heart of any chemical transformation. These processes are essential prerequisites for a chemist to venture into the synthesis of simple or complex molecules. Most of the biologically active molecules contain carbon-heteroatom bond, and their formation goes on continuously *in vivo* involving C—C bond cleavage. However, *in vitro* chemoselective cleavage of C—C bond has always been the challenging task due to its inherent inert nature, thermodynamic stability and uncontrollable selectivity.[1] The cleavage of carbon-carbon bonds and the simultaneous formation of carbon-heteroatom bonds facilitates reorganization of an organic structure to new ones. Conventional methods for the cleavage of inert C—C bonds make use of harsh conditions with stoichiometric oxidants such as peroxides and toxic metal salts.[2] Therefore, it is highly desirable and challenging to develop milder, more efficient and general protocols for the cleavage of C—C bonds.

The pivotal example of C—C bond cleavage dates back more than a half century. In the recent literature, many reactions have been reported that involve formal C(CO)—C(α) bond cleavage with transition-metal based catalysts.[3] Recently, Bathula and co-workers[4a] reported iodine-catalyzed oxidative C—C bond cleavage of alkyl aryl ketones resulting to aromatic acids and amides. Jiang et al.[4b] demonstrated oxidative cleavage and esterification of C—C bond of α-hydroxy ketones using K_2CO_3 and [18]-crown-6. Paine and co-workers[4c] reported the similar cleavage of aryl-α-hydroxyketones using enzymes for the synthesis of corresponding acids. Murakami and Ishida[4d] recently reported the potential of metal-catalyzed C—C single bond cleavage for organic synthesis. Wang and co-workers[4e] reported two well-controlled transformations of β-oxodithioesters with hydroxylamine to afford β-ketonitriles and isoxazoles, respectively, under different reaction conditions. However, the use of expensive and toxic metals along with equivalent amounts of oxidants limits the application of such protocols in organic synthesis. Consequently, development of metal-free and catalyst-free strategies to cleave C—C bond is a better alternative for synthetic manipulations.

Polyfunctional simple molecule β-ketodithioester (KDTE) has received significant attention in organic synthesis as a key substrate.[5] During the recent past, our group focused on the reactivity of β-ketodithioesters for the construction of skeletally distinct heterocyclic frameworks *via* domino protocols.[6] Recently, we reported selective cleavage of $C(sp^3)$—$C(sp^3)$ bond of β-allyl-β-hydroxydithioesters catalyzed by $Y(OTf)_3$.[7] To our knowledge, examples of metal-free C—C bond cleavage of β-ketodithioesters are rare. Consequently, exploring the metal-free and catalyst-free protocol for C—C bond cleavage of β-ketodithioesters continues to be a challenging and valuable target. Prompted by our previous

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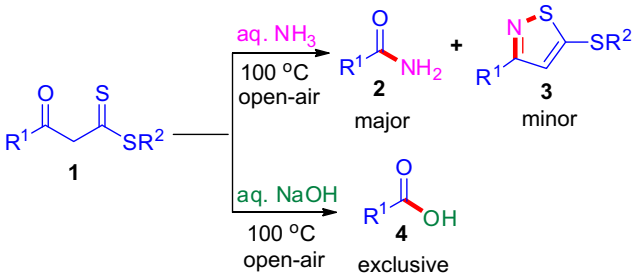


Scheme 1. Formation of amides, isothiazoles and acids from β-ketodithioesters.

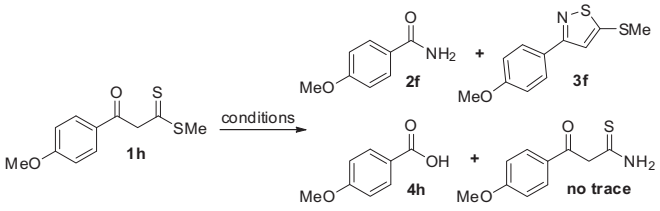
report, and as a part of ongoing synthetic quest to expand the frontiers of β-ketodithioester chemistry, we wish to disclose an expedient synthesis of aromatic acids, aromatic amides and isothiazoles from a common dithioester precursor *via* operationally simple one-pot cascade process. To the best of our knowledge, no report is available until date for the formation of amides and acids from β-ketodithioesters.

The demand for improved synthetic methods toward aromatic amides and aromatic acids is high and continuous. It is noteworthy that amides and acids are the chief functionalities of alkaloids, antibiotics, amino acids, vitamins, protein, nucleic acids, neurotransmitters and polymers. They have been widely utilized in strategic synthesis enabling their tremendous application in industry and pharmaceutical chemistry. The aromatic amide foldamers are widely exploited for molecular recognition, as these conformationally flexible aromatic amide oligomers act as receptor.[8] Therefore, the development of efficient alternative route to prepare such compounds always remains a regular practice to synthetic chemists. In this regard, we herein disclose a metal-free, catalyst-free and oxidant-free protocol for the cleavage of C—C bond of β-ketodithioesters for the first time (Scheme 1). This transformation has wide substrate scope and proceeds with excellent chemoselectivity.

β-Ketodithioesters are not available commercially, but can be easily synthesized from the reaction of enolates with trithiocarbonate by literature method.[9] Prompted by the awe-inspiring chemistry of β-ketodithioesters, we envisioned that treatment of β-ketodithioester with ammonia should form β-ketothioamide.[6h] Subsequently, we treated β-ketodithioester **1h** (1 mmol) as a model substrate with the aqueous ammonium hydroxide (25%, 10 ml) as a source of ammonia at room temperature. After 24 h of stirring, work up of the reaction mixture, unexpectedly provided two products which were characterized as 4-methoxybenzamide **2f** in 35% yield and 3-(4-methoxyphenyl)-5-thiomethyl isothiazole **3f** in 8% yield by comparison with the reported ones.[6d] To our surprise, we did not get even a trace of β-ketothioamide (Table 1, entry 1). We thought increase in temperature may furnish the desired thioamide, so, we performed the reaction at elevated temperatures. Reaction at 60 °C increased the yield of 4-methoxybenzamide **2f** to 56% with no trace of thioamide (Table 1, entry 2). Then, the above result encouraged us to optimize the conditions for the formation of 4-methoxybenzamide **2f** in high yield. In this context, we performed the above model reaction at 100 °C. To our pleasure, we obtained the desired amide **2f** in 88% yield within 12 h (Table 1, entry 3). However, the above both conditions could not increase the yield of isothiazole **3f**.

Inspired by the literature report,[10] to increase the yield of isothiazole, we treated dithioester **1h** with a mixture of aq. NH_4OH (25%) and 1 equiv of $Cu(OAc)_2$ at room temperature. The reaction completed within 1 h forming Cu-dithioester complex as a major product with a trace amount of both amide and isothiazole (Table 1, entry 4).[11] When **1h** was treated with 8 N NaOH and 1 equiv of $Cu(OAc)_2$ at room temperature, similar result was obtained as in entry 4, except reaction took longer time to complete (Table 1, entry 11).

Table 1
Optimization of reaction conditions.[a]



Entry	Base (10 ml)	Promoter (1 equiv)	Temp (°C)	Time (h)	Yield (%)[b]		
					2f	**3f**	**4** h
1	NH_4OH (25%)	nil	rt	24	35	8	nil
2	NH_4OH (25%)	nil	60	18	56	7	nil
3	NH_4OH (25%)	nil	100	12	88	5	nil
4	NH_4OH (25%)	$Cu(OAc)_2$	rt	1	trace	trace	–[c]
5	NH_4OH (25%)	$Cu(OAc)_2$	60	8	45	15	–[c]
6	NH_4OH (25%)	$Cu(OAc)_2$	100	6	50	20	–[c]
7	NaOH (2 N)	nil	100	24	nil	nil	trace
8	NaOH (4 N)	nil	100	24	nil	nil	55
9	NaOH (8 N)	nil	100	10	nil	nil	98
10	KOH (8 N)	Nil	100	10	nil	il	86
11	NaOH (8 N)	$Cu(OAc)_2$	rt	6	nil	nil	–[c]

[a] 1.0 mmol of **1h** and 10 ml of each base were used.
[b] Isolated yield.
[c] Copper complex with dithioester was formed as major product.[11]