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Metal- and Catalyst-Free, Formal [4 + 1] Annulation via Tandem C═O/C═S Functionalization: One-Pot Access to 3,5-Disubstituted/Annulated Isothiazoles

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Supporting Information

ABSTRACT: An operationally simple and user-friendly new protocol for the synthesis of 3,5-disubstituted/annulated isothiazoles is devised utilizing β-ketodithioesters/β-ketothioamides and NH_4OAc via C═O/C═S bond functionalization under metal- and catalyst-free conditions. The strategic [4 + 1] annulation initiated by NH_4OAc is carbon-economic and relies on a sequential imine formation/cyclization/aerial oxidation cascade forming consecutive C−N and S−N bonds in one pot. A wide range of previously inaccessible and synthetically challenging isothiazoles are compatible with this transformation under nontoxic conditions with excellent functional group tolerance. The products bear useful synthetic handles for further functionalization.

Isothiazoles are valuable either as synthetic intermediates or in biological/industrial applications.[1,2] The commercial importance of isothiazole derivatives has been established in their use as artificial sweeteners and kathon preservatives.[3] Sulfasomizole (**I**) and denotivir (**II**), both having isothiazole skeletons, display antibacterial and antiviral properties, respectively.[4] In addition, isothiazole derivatives are well-known in drug discovery due to their significant biological activities such as analgesic, antipyretic, fungicidal, and herbicidal properties.[5] In particular, the 3,5-disubstituted isothiazole skeleton is a key structural unit that appears in the core structures of pharmaceutically relevant molecules such as GPR agonists[6] (**III**), mGluR1 antagonists[7] (**IV**), potent inhibitors of aurora kinase[8] (**V**), antipsychotic zipracidone (**VI**), and tyrosine kinase c-Met[9] (**VII**) (Figure 1). GPR agonists have a tendency to improve the triglyceride level of cell membranes and also act as an insulin regulator, while mGluR1 antagonists have proven useful in modulating nociception preclinically. Some isothiazole derivatives have been used as corrosion inhibitors[10a] and antifreeze compositions for diesel engines.[10b] The 4-cyanoisothiazoles are used as inkjet inks and dyes.[10c] The present popularity of the isothiazoles is mainly due to their close structural relationship to some clinically important inhibitors of HIV-1, and this would open the door for many organic chemists to challenges in the areas of synthetic organic and medicinal chemistry.

As a consequence, much attention has been paid to the synthesis of isothiazole derivatives.[11] Though metal-catalyzed reactions have been occupying a dominant position in organic synthesis, the use of metal-free and catalyst-free reactions would be arguably considered to be environmentally friendly. Most of these metal-catalyzed reactions involve specially designed ligands or well-defined catalysts/reagents, which increase the cost and limit the scope of applications. Cascade processes that incorporate multiple bond-forming events in one pot have come into play and are of paramount interest in organic

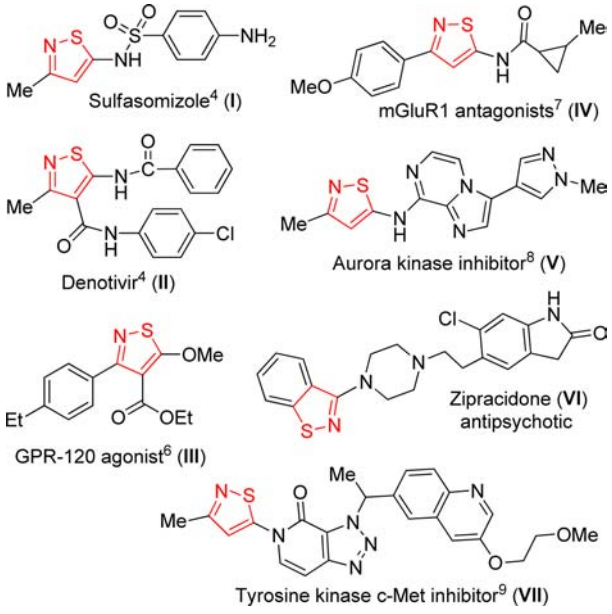

Figure 1. Some biologically active compounds containing the isothiazole moiety.

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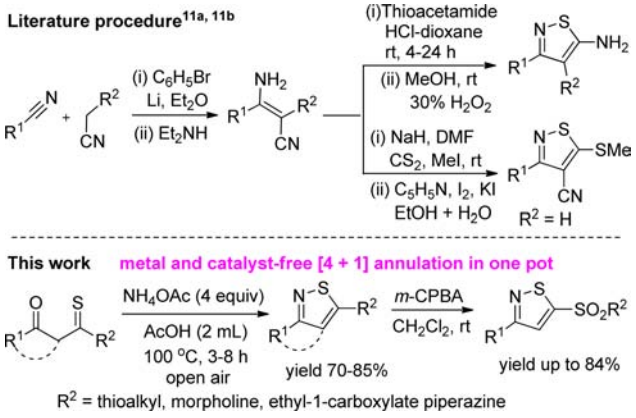
synthesis.[12] Efficiency and environmental sustainability are central issues in contemporary organic synthesis.

Our group has a long-standing interest in exploiting the reactivity of β-ketodithioesters (KDTEs) under eco-friendly conditions.[13] These protocols construct a number of important heterocyclic scaffolds; however, the synthesis of isothiazole from KDTEs has not been yet explored. Recently, Li and co-workers[14] reviewed the chemistry of β-ketothioamides (KTAs) as versatile building blocks for various heterocycles, which also does not include isothiazole. As a continuation of our ongoing research interest toward the synthesis of thiadiazoles, isoxazoles, and pyrazoles utilizing KDTEs,[15] herein we report the first concise example of a metal- and catalyst-free tandem annulation of KDTEs with cheap and easily available NH_4OAc to construct the isothiazole skeleton in good yield (Scheme 1). Striking features of this simple and efficient annulating approach include a challenging C═O/C═S bond functionalization with excellent functional group tolerance.

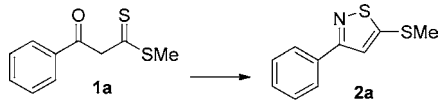
Scheme 1. Strategies toward Isothiazoles



Among available reports to access isothiazole derivatives,[11,16] most of them suffer from significant limitations such as toxic and expensive reagents, multiple steps, and poor availability of starting materials. Therefore, it is still highly desirable to explore operationally simple, efficient, and widely applicable approaches to the synthesis of isothiazoles. The C−N and S−N bond formations constitute a very important class of reactions in biological processes. To the best of our knowledge, no report on the synthesis of isothiazoles utilizing KDTEs is known to date. With this in mind, we envisioned the feasibility of annulating KDTEs with NH_4OAc (source of NH_3) to construct the framework of isothiazoles. To establish the viability of our new concise approach, we intensively investigated the model reaction of methyl-3-oxo-3-phenylpropanedithioate **1a** with NH_4OAc in open air, and the results are listed in Table 1.

Initially, we performed the reaction of **1a** (1 mmol) with NH_4OAc (2 equiv) in AcOH (2 mL) at room temperature; no trace of the product was obtained even after 24 h, and **1a** remained completely unconsumed (Table 1, entry 1). To check the effect of temperature on the reaction, the test reaction was carried out at different temperatures (Table 1, entries 2−5). It has been found that maximum conversion occurred at 100 °C, providing the desired product **2a** in 60% yield after 24 h (Table 1, entry 4). Higher temperature (120 °C) made the reaction messy, and product **2a** was obtained only in 46% yield (Table 1, entry 5). To improve the efficiency of the reaction further, we performed the reaction with 4 equiv of NH_4OAc at 100 °C. In this manner, the desired product **2a** was obtained in 75% yield within 7 h (Table 1, entry 6).

Table 1. Optimization Conditions[a]



entry	ammonium salt (equiv)	solvent	temp (°C)	time (h)	yield[b] (%)
1	NH_4OAc (2)	AcOH	rt	24	–
2	NH_4OAc (2)	AcOH	50	24	50
3	NH_4OAc (2)	AcOH	80	24	55
4	NH_4OAc (2)	AcOH	100	24	60
5	NH_4OAc (2)	AcOH	120	24	46
6	NH_4OAc (4)	AcOH	100	7	75
7	$(NH_4)_2CO_3$ (4)	AcOH	100	12	65
8	HCO_2NH_4 (4)	AcOH	100	12	62
9	NH_4OAc (4)	MeOH	reflux	12	39
10	NH_4OAc (4)	EtOH	reflux	12	46
11	NH_4OAc (4)	H_2O	100	12	trace
12	NH_4OAc (4)	MeOH + H_2O	100	12	30[c]
13	NH_4OAc (5)	AcOH	100	7	75

[a]Reaction conditions: all of the reactions were performed with **1a** (1 mmol) and NH_4OAc (4 equiv) in 2 mL of solvent at 100 °C in open air. [b]Isolated yield. [c]1:1 mixture of MeOH and H_2O.

The success of this protocol prompted us to investigate some other ammonium salts such as $(NH_4)_2CO_3$ and HCO_2NH_4, but no improvement was observed (Table 1, entries 7 and 8). Next, screening of other protic polar solvents such as methanol, ethanol, and water also did not provide better results (Table 1, entries 9−11). Mixtures of methanol and water also did not improve the outcome of the reaction (Table 1, entry 12). Further, increasing the amount of NH_4OAc did not improve the efficiency of the reaction (Table 1, entry 13). Thus, the optimum conditions for the synthesis of isothiazole **2a** were achieved by employing **1a** (1 mmol) and NH_4OAc (4 equiv) in 2 mL of AcOH at 100 °C in open air (Table 1, entry 6).

With the established optimal conditions, we then set out to explore the scope of this reaction by allowing a variety of structurally diverse β-ketodithioesters **1** to react with NH_4OAc; the results are summarized in Schemes 2 and 3. The influence of substituents in the phenyl ring (R^1 moiety) of KDTEs **1** was first investigated. The variants of the substituents did not hamper the reaction process. This new annulation tolerated KDTEs **1** bearing both electron-donating and electron-withdrawing groups under the optimized reaction conditions. However, KDTEs bearing electron-donating groups took somewhat longer than those bearing electron-withdrawing groups (Scheme 2, **2b−d** vs **2e−g**). This could be due to increased electron density on the carbonyl carbon in the former substrates which decreases the rate of imine formation (in situ condensation of NH_3 with C═O of KDTE). Various substituents on the phenyl ring (R^1) such as Me, OMe, OCH_2O, Cl, Br, and CF_3 were found to be compatible.

Even a challenging case in which a strong electron-withdrawing effect of CF_3 exists on the *para*-position was also well suited for this annulation, providing the corresponding product **2f** in 85% yield within 5 h. Moreover, the more sterically demanding *o*-bromo substituent was successfully engaged in this reaction (Scheme 2, **2g**). Importantly, KDTEs bearing heteroaromatic moieties such as 2-furyl and

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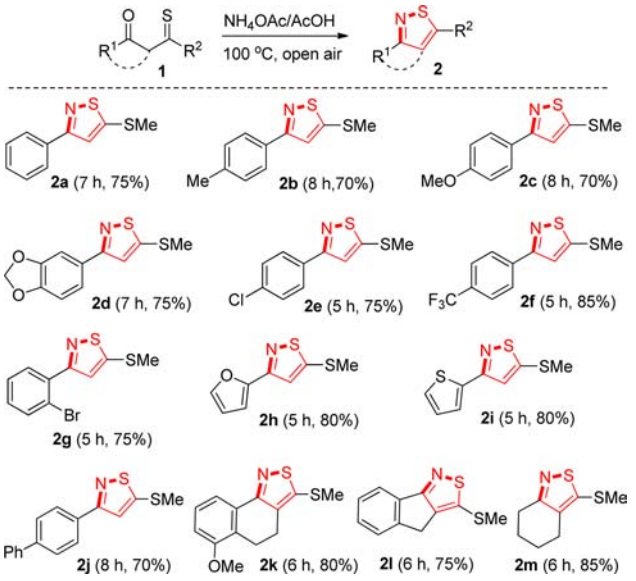
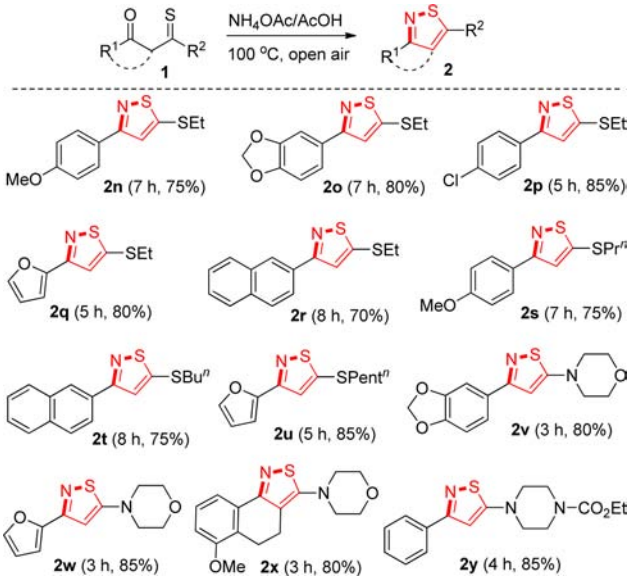
Scheme 2. Substrate Scope for the Syntheses of 2a−m



Scheme 3. Substrate Scope To Access Isothiazoles 2n−y

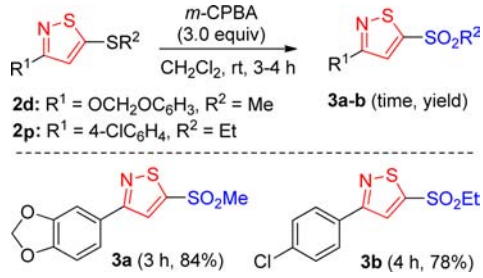


2-thienyl at R^1 were also well tolerated and furnished the corresponding isothiazoles in 80% yields (Scheme 2, **2h−i**). It is noteworthy that KDTEs bearing not only aromatic and heteroaromatic R^1 moieties but extended aromatics also worked well under the optimized conditions (Scheme 2, **2j**, and Scheme 3, **2t**). The scope and generality of this one-pot cascade procedure was further evident by synthesis of annulated isothiazoles **2k−m** as shown in Scheme 2. Thus, treatment of KDTEs **1k−m**, derived from 1-tetralone, indanone, and cyclohexanone, respectively, with NH_4OAc under standard conditions provided the corresponding annulated isothiazoles **2k−m** in 75−85% yields.

After the successful utilization of the R^2 moiety as the SMe group, we next extended our studies toward synthesis of isothiazoles bearing different substituents at the R^2 moiety. Our studies revealed that KDTEs **1** bearing different substituents at R^2 such as SEt, SPr^n, SBu^n, and SPentyl^n were also tolerated well and furnished the corresponding isothiazoles in 70−85% yields (Scheme 3, **2n−u**). Further, β-ketothioamides bearing morpholine and ethyl 1-carboxylate piperazine as the R^2 substituent also enabled the reaction to occur smoothly, resulting in the corresponding 5-(cycloamino)isothiazoles in 80−85% yields (Scheme 3, **2v−y**). The chemistry is amenable to both small- and large-scale reactions. To demonstrate the utility of this protocol, a large-scale experiment (**1o**, 10 mmol, 2.68 g) was carried out under the standard conditions. The reaction proceeded smoothly, providing the desired isothiazole **2o** in 76% (2.01 g) isolated yield, which is comparable to the small scale experiment (Scheme 3, **2o**, 80%).

After the effective synthesis of diverse isothiazoles **2**, we extended our study toward further functionalization of **2**. Due to the immense importance of alkylsulfonyl derivatives of heterocycles in the medicinal field,[17] we thought to functionalize the 5-thioalkyl group to alkylsulfonyl derivatives. The alkylsulfonyl compounds can improve pharmacological properties compared to their nonsulfonyl analogues. Subsequently, we treated compounds **2d** and **2p** separately with 3 equiv of *m*-CPBA in CH_2Cl_2 at room temperature. The reaction proceeded well, affording the corresponding sulfonyl derivatives **3a** and **3b** in good yields (Scheme 4).

Scheme 4. Functionalization of Isothiazoles



The structural elucidation of all the newly synthesized compounds **2a−y** and **3a−b** was determined by satisfactory spectral (^{1}H, ^{13}C NMR and HRMS) studies. Furthermore, the structure of **2o** was unequivocally confirmed by single-crystal X-ray diffraction analysis (Figure 2; see the Supporting Information).[18]

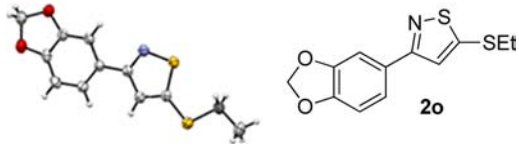
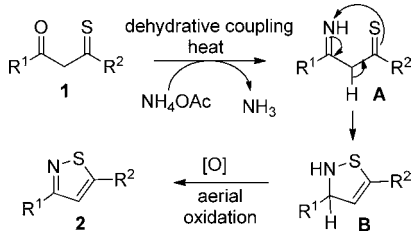


Figure 2. ORTEP diagram of **2o** (CCDC 1469295).

On the basis of the above analysis and literature reports, a plausible reaction scenario is outlined in Scheme 5. The first

Scheme 5. Proposed Mechanism for the Formation of 2



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step involves the selective nucleophilic attack of ammonia (generated in situ from NH_4OAc) at the carbonyl carbon of **1** to give imine intermediate **A**, which undergoes intramolecular nucleophilic attack of sulfur on the imine nitrogen, forming the S−N bond to generate cyclic intermediate **B**. Subsequent aerial oxidation of intermediate **B** gives the desired isothiazole **2**.

In summary, we have developed a new one pot cascade C−N and N−S bond formation that offers efficient construction of 3-aryl-5-thioalkyl/cycloamino-substituted/annulated isothiazoles via metal-free and catalyst-free formal [4 + 1] annulation of *β*-ketodithioesters/*β*-ketothioamides with NH_4OAc. Ammonium acetate plays a dual role as a source of ammonia and base. The reaction pathway involved an imine formation/cyclization/aerial oxidation sequence, leading to the elegant assembly of functionalized isothiazoles. Nontoxic conditions, flexible structural modification, broad substrate scope, and good functional group tolerance as well as further functionalization to sulfonyl derivatives make this strategy highly viable for future applications. The described open-flask cascade chemistry is general, eco-compatible,and low cost, making this protocol a good alternative to existing ones.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00997.

X-ray crystallographic data for **2o** (CIF)

Experimental procedure, full characterization of products, and ^{1}H NMR, ^{13}C NMR, and HRMS spectra (PDF)

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Notes

The authors declare no competing financial interest.

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