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I_2/TBHP-Mediated tandem cyclization and oxidation reaction: Facile access to 2-substituted thiazoles and benzothiazoles†

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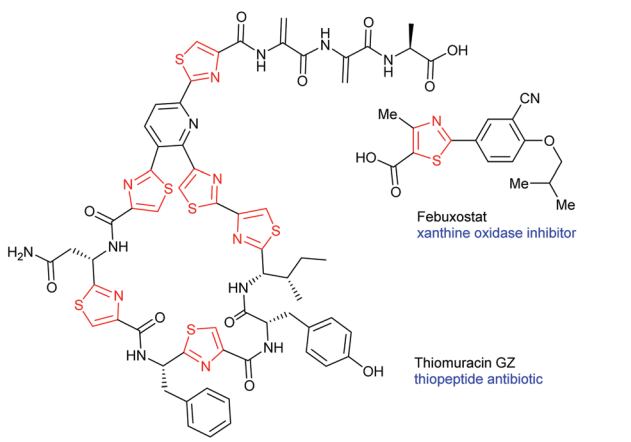
The efficient synthesis of 2-substituted thiazoles and benzothiazoles has been accomplished employing readily available cysteine esters and 2-aminobenzenethiols as N and S sources. The reaction proceeds under an I_2/TBHP system and involves a one-pot tandem cyclization and oxidation sequence. A diverse range of aldehydes is amenable for this transition-metal-free protocol, which provides an alternative method to rapidly access thiazole-containing molecules.

Thiazole and its derivatives are ubiquitous components of biological natural products.[1] Based on extensive research by medicinal chemists, many thiazole-containing molecules have displayed promising pharmacological activities.[2] These valuable structural subunits are also broadly employed in the development of novel active pharmaceutical ingredients due to their unique ability to impact therapeutic potency, drug lipophilicity, *etc*.[2] For instance, febuxostat, a drug used in the treatment of chronic gout and hyperuricemia, functions as a selective inhibitor of xanthine oxidase, whereas thiomuracin GZ, a member of the thiopeptide antibiotic family with potent activity toward Gram-positive drug-resistant bacteria, possesses several distinct thiazole scaffolds (Scheme 1).[3] Moreover, they also play an increasingly important role in materials chemistry as the core components of materials with optical or electronic properties.[4]

The strong demand for this heterocyclic scaffold has stimulated much effort. Classical methods to assemble such motifs rely on the cyclization strategy, and are exemplified by Hantzsch's synthesis, the Gabriel synthesis, and the Cook–Heilbron synthesis.[1] Besides, the direct oxidation of pre-synthesized thiazolines to substituted thiazoles was also reported with various oxidants including MnO_2, DDQ, *etc*.[5] In spite of some advantages, the methods described above often encounter certain limitations including harsh reaction conditions, expensive toxic metals/oxidants, tedious synthetic procedures toward starting materials, and release of toxic by-products. Therefore, the pursuit of alternative efficient protocols to obtain thiazoles has never ceased.

Given our group's long-term interest in heterocyclic chemistry and green chemistry,[6] we questioned whether simple natural amino acids could be employed as the nitrogen and sulfur sources for thiazole synthesis. More specifically, we planned to realize the synthesis by developing a tandem imine formation, intermolecular cyclization and oxidation protocol.[7] Furthermore, the ester group could serve as a useful synthetic handle to accomplish the facile synthesis of other useful thiazole-based derivatives. Nevertheless, a critical task for developing this protocol would be the identification of compatible cyclization and oxidation conditions for this transformation.[8] Also, the employment of transition metals and toxic oxidants should also be avoided. Despite these challenges, we herein would like to report our recent efforts in developing an



Scheme 1 Thiazole-based bioactive molecules.

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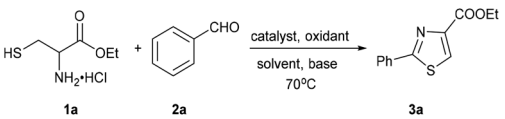
efficient tandem cyclization/oxidation protocol employing I_2 and *tert*-butyl hydroperoxide (TBHP) to synthesize thiazole derivatives. This methodology was amenable for a large range of readily available aldehydes.[9] Due to the immense usefulness of 2-substituted thiazole motifs, this protocol in principle should be of great interest to the community.[10]

To investigate our proposed reaction, initial studies focused on the reaction between L-cysteine ethyl ester hydrochloride (**1a**) and benzaldehyde (**2a**), as shown in Table 1. We were delighted to discover that the ethyl 2-phenylthiazole-4-carboxylate (**3a**) is formed in the presence of potassium iodide and *tert*-butyl hydroperoxide (TBHP) in 41% yield (entry 1). Other iodine-based catalysts were also evaluated, and the yields could be improved to 58% when employing iodine as the catalyst (entries 2–5). Oxidants including benzoyl peroxide, di-*tert*-butyl peroxide and hydrogen peroxide were evaluated subsequently, but none of them afforded more satisfactory results (entries 6–8). Additional assessment of the base effect indicated that potassium carbonate was the best condition for this transformation, providing a higher chemical yield (entry 2 *vs.* entries 9 and 10). A significant increase in the reaction outcome was observed upon switching the solvent to 1,4-dioxane. Other commonly used solvents (entries 12 and 13) showed no improvements. Next, the essential roles of the catalyst and oxidant were demonstrated by control experiments, wherein minimal amounts of **3a** were detected (entries 14 and 15). Finally, the investigation revealed that the chemical yield of **3a** could be improved to 90% under a nitrogen atmosphere (entry 16).

Table 1 Reaction condition optimization[a]



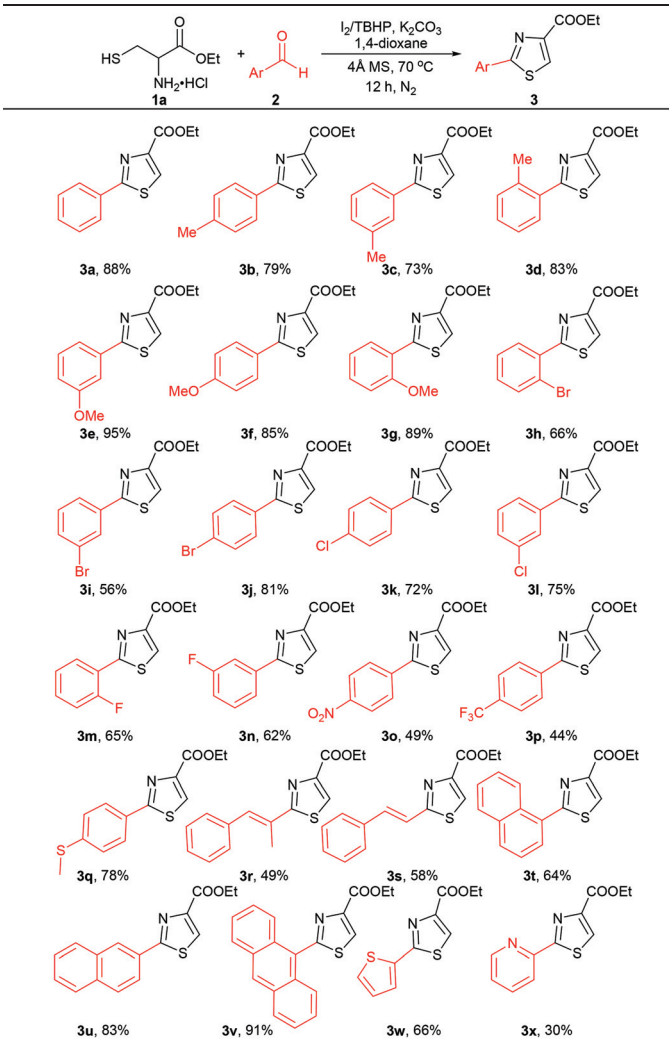
1a 2a 3a

Entry	Catalyst	Oxidant	Solvent	Yield[b]
1	KI	TBHP	DMF	41%
2	I_2	TBHP	DMF	58%
3	NH_4I	TBHP	DMF	44%
4	NaI	TBHP	DMF	39%
5	NIS	TBHP	DMF	46%
6	I_2	BPO	DMF	44%
7	I_2	DTBP	DMF	52%
8	I_2	H_2O_2	DMF	53%
9[c]	I_2	TBHP	DMF	27%
10[d]	I_2	TBHP	DMF	37%
11	I_2	TBHP	1,4-Dioxane	85%
12	I_2	TBHP	DMSO	22%
13	I_2	TBHP	CH_3CN	43%
14	—	TBHP	1,4-Dioxane	7%
15	I_2	—	1,4-Dioxane	Trace
16[e]	I_2	TBHP	1,4-Dioxane	90 (88%)[f]

[a] **1a** (0.4 mmol), **2a** (0.1 mmol), I_2 (0.03 mmol), TBHP (0.4 mmol), K_2CO_3 (0.3 mmol), 4 Å MS (0.2 g) and solvent (0.5 mL) for 12 h. [b] Yield determined by ^1H NMR with 1,3,5-trimethoxybenzene as an internal standard. [c] $NaHCO_3$ was used instead. [d] Cs_2CO_3 was used instead. [e] N_2 atmosphere. [f] Isolated yield (NIS: *N*-iodosuccinimide; BPO: benzoyl peroxide; DTBP: di-*tert*-butyl peroxide).

Given these results, we next explored the substrate scope of aldehyde components using the optimized reaction conditions (Table 2). A wide range of aromatic aldehydes were found to display comparable reactivities to benzaldehydes, giving the desired substituted thiazoles in good yields (**3b–3p**). In general, the electron-donating groups are well tolerated providing the structurally diverse thiazoles in good yields, whereas the electron-withdrawing substitution groups gave slightly lower yields. Notably, the sulfide functionality was well tolerated due to which **3q** was produced with a yield of 78%, even though sulfides are known to be easily converted into sulfoxides under oxidative conditions.[11] Furthermore, aldehydes bearing poly-aromatic rings and conjugated systems were also compatible with this transformation, giving the thiazole products (**3r–3v**) in good yields. Given the importance of heterocycles in the production of functional molecules, we were delighted to find that 2-thienylaldehyde and 2-pyridinecarbox-

Table 2 Substrate scope[a,b]



[a] **1a** (0.8 mmol), **2** (0.2 mmol), I_2 (0.06 mmol), TBHP (0.8 mmol), K_2CO_3 (0.6 mmol), 4 Å MS (0.4 g) and 1,4-dioxane (1 mL) under a N_2 atmosphere, 70 °C, 12 h. [b] Isolated yield.

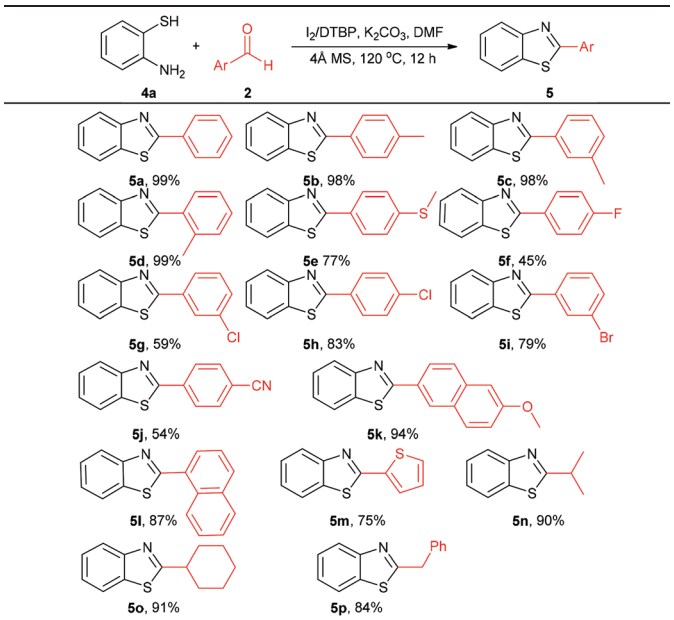
aldehyde readily participate in this reaction to give the desired products in 66% and 30% yield, respectively. When the aliphatic aldehyde such as isobutyraldehyde was employed, no desired product was observed, which demonstrated a limitation of our protocol.

Although initial studies focused on using cysteine as the N and S sources for thiazole synthesis, we next wondered whether 2-aminobenzenethiol would be a suitable reaction component (Table 3). Indeed, this domino process could also furnish the benzothiazoles (**5a–5p**) in good yields under similar reaction conditions. Noteworthily, a similar trend of electronic effects was observed in which aldehydes with electron-withdrawing substitution groups gave slightly lower yields than those with electron-donating groups. Aliphatic aldehydes, on the other hand, proved to be tolerated for benzothiazole synthesis due to which products **5n–5p** were obtained in good yields. Given the fact that thiazoles and benzothiazoles are commonly found in pharmaceutically relevant compounds, our protocol should be attractive to the community.[10,12]

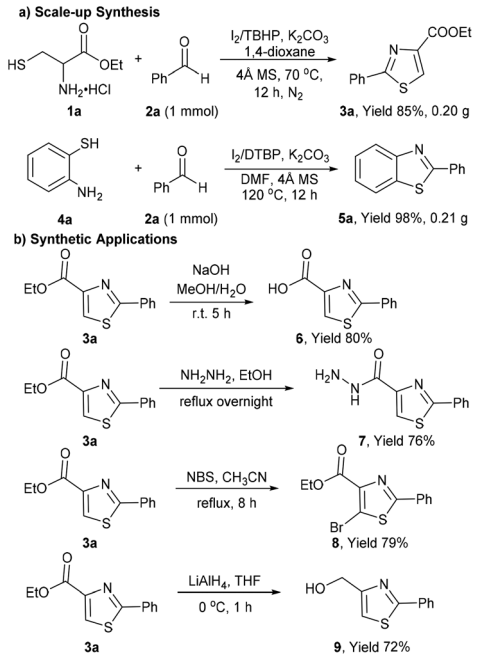
This thiazole synthesis protocol is amenable for scale-up preparation (Scheme 2). We reacted 1.0 mmol of **2a** with excess **1a** or **4a** under the standard reaction conditions, and products **3a** and **5a** were produced in 85% and 98% yields, respectively. The functionalization of **4a** has also been successfully achieved to provide the thiazole-containing products **6–9**. These derivatizations could further offer pathways to a number of useful thiazole-containing compounds, further highlighting the synthetic advantages of our method.[1]

To gain insights into the reaction mechanism, control experiments were performed accordingly (Scheme 3). When

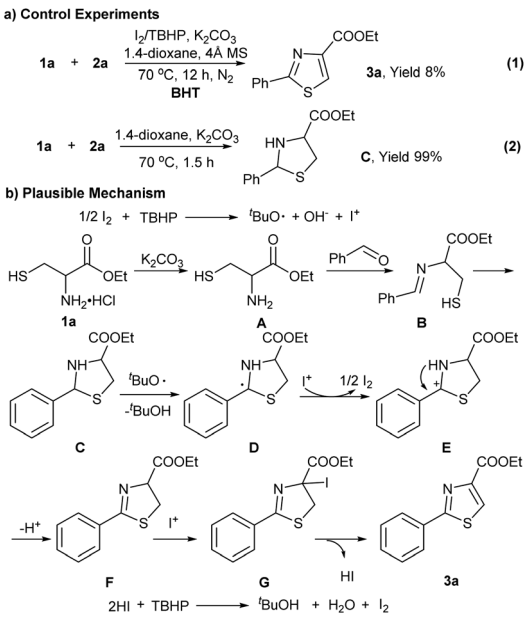
Table 3 Substrate scope[a,b]



[a] **4a** (0.8 mmol), **2** (0.2 mmol), I_2 (0.06 mmol), DTBP (0.8 mmol), K_2CO_3 (0.6 mmol), 4 Å MS (0.4 g) and DMF (0.4 mL) at 120 °C for 12 h. [b] Isolated yield.



Scheme 2 Synthetic applications.



Scheme 3 Mechanistic studies.

excess radical scavenger BHT was added to the model reaction, the desired thiazole product was obtained with only 8% yield, indicating that our method might take place through a radical pathway. Compound **C** could be obtained under the sole basic conditions *via* cyclization. Besides, in the absence of iodine, **3a** was not obtained, whereas NIS as the catalyst gave the desired thiazole product with 46% yield (Table 1, entries 5 and 14). Therefore, an I_2–I^+ redox process might be involved in our protocol. Based on these results and literature reports,[13] a

plausible mechanistic pathway for our I_2/TBHP-promoted ring cyclization and oxidation reaction cascade is depicted in Scheme 3. In the presence of potassium carbonate, the cysteine ester initially underwent tandem imine formation and cyclization to give intermediate **C**. Under the I_2/TBHP catalyst system, compound **C** is converted to give partially oxidized intermediate **F** *via* a sequence of hydrogen abstraction, single electron transfer with I^+ and elimination. Next, the I^+ species, generated by the oxidation of iodine, could react with intermediate **F** and subsequent elimination of **G** to give the final product **3a**.

Conclusions

In summary, we developed an efficient one-pot cascade cyclization/oxidation approach to synthesize substituted thiazoles and benzothiazoles from readily available starting materials. This catalytic protocol avoids using transition metal oxidants and shows a broad substrate scope, providing consistently good yields of thiazole products. Remarkably, the reaction proved to be not only efficient in scale-up reactions, but further functionalization was also easily possible, setting the base for rapidly accessing medicinally relevant thiazole derivatives. In comparison with the classical approaches, we anticipate that our method should provide a potential alternative.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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