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Cu-Catalyzed Aerobic Oxidative Sulfuration/Annulation Approach to Thiazoles via Multiple Csp^3−H Bond Cleavage

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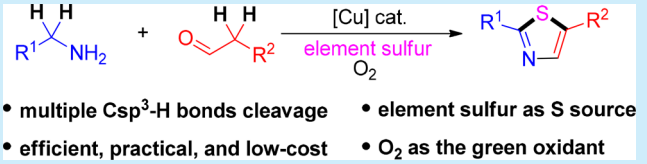
Supporting Information

ABSTRACT: A novel and practical Cu-catalyzed aerobic oxidative synthesis of thiazoles was developed. This chemistry for the first time achieved thiazole construction from simple aldehydes, amines, and element sulfur through multiple Csp^3−H bond cleavage processes. Molecular oxygen was used as a green oxidant in this oxidative protocol. The substrate scope is broad with the tolerance of aliphatic amines. The mechanistic study might promote the reaction design for a new sulfuration/annulation reaction with readily available element sulfur.



Thiazoles are very important compounds and ubiquitous structural motifs found in biologically active molecules, pharmaceuticals, and functional materials (Figure 1).[1] In the past decades, by using the cheap, stable, nontoxic, and nonsmelly element sulfur reagent, the sulfurations of functionalized substrates for the synthesis of sulfur-containing heterocycles have been well developed.[2] Recently, with the development of C−H bond functionalization,[3] the direct C−H sulfuration has been an attractive strategy for the synthesis of sulfur-containing compounds.[4] So far, the C−H sulfuration and annulation with element sulfur reagent is still a challenging issue and therefore highly desired.

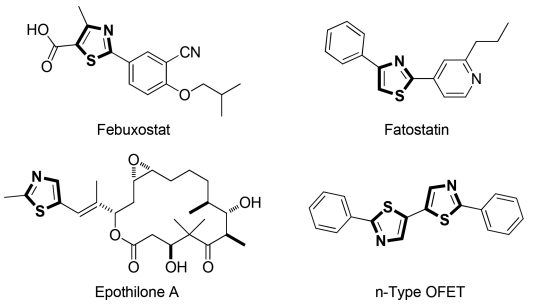
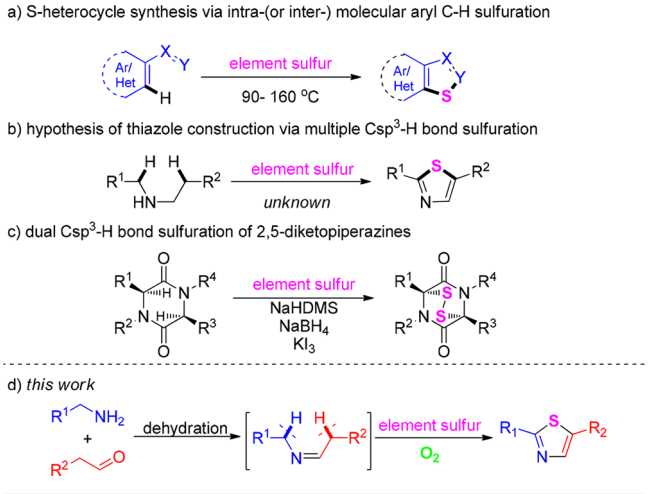


Figure 1. Thiazoles as core structures in compounds.

More recently, by using the aryl or heteroaryl Csp^2−H bond sulfuration strategy (Scheme 1a), several sulfur-containing heterocycles such as thiophenes, benzothiazoles, benzoisothiazolones, and thienoindoles were significantly constructed through an intra- or intermolecular sulfuration/annulation reaction by the groups of Itami,[5a] Deng,[5b] Shi,[5c] Deng,[5d−f] and Li.[5g] In contrast to the significance of Csp^2−H sulfuration, the Csp^3−H sulfuration was rarely achieved.[6] To the best of our knowledge, the important thiazole construction through multiple Csp^3−H bond cleavages from readily available substrates remains unknown and is urgently desired (Scheme 1b). Notably, Nicolaou and co-workers reported a novel one-pot tandem strategy for the introduction of sulfur into cyclic 2,5-diketopiperazines for the synthesis of epidithiodiketopiperazines via two Csp^3−H bond sulfurations (Scheme 1c).[6]

Scheme 1. Hypothesis for the Thiazole Construction through Multiple Csp^3−H Sulfuration/Annulation



Inspired by these reactions, we envisioned that Csp^3−H bonds of both amine and acetaldehyde would undergo sulfuration to form C−S bonds for the construction of thiazoles (Scheme 1d). However, there are two main challenges in this multiple Csp^3−H dehydrogenative sulfuration/annulation hypothesis: (1) Sulfur might poison the transition metal

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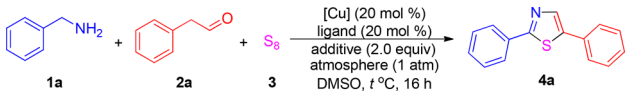
Table 1. Optimization of the Reaction Conditions[a]



entry	[Cu]	additive	ligand	atmosphere	t (°C)	**4a** yield (%)
1	$CuBr_2$	-	-	air	80	40
2	$Cu(OTf)_2$	-	-	air	80	34
3	$Cu(OAc)_2$	-	-	air	80	29
4	$CuBr_2$	PivOH	-	air	80	trace
5	$CuBr_2$	DABCO	-	air	80	28
6	$CuBr_2$	DBU	-	air	80	52
7	$CuBr_2$	DBU	-	O_2	80	65
8	$CuBr_2$	DBU	-	O_2	100	64
9	$CuBr_2$	DBU	TMEDA	O_2	80	60
10	$CuBr_2$	DBU	Py	O_2	80	61
11	$CuBr_2$	DBU	bPy	O_2	80	58
12	$CuBr_2$	DBU	1,10-phen	O_2	80	76
13[b]	$CuBr_2$	DBU	1,10-phen	O_2	80	78
14	-	DBU	1,10-phen	O_2	80	0

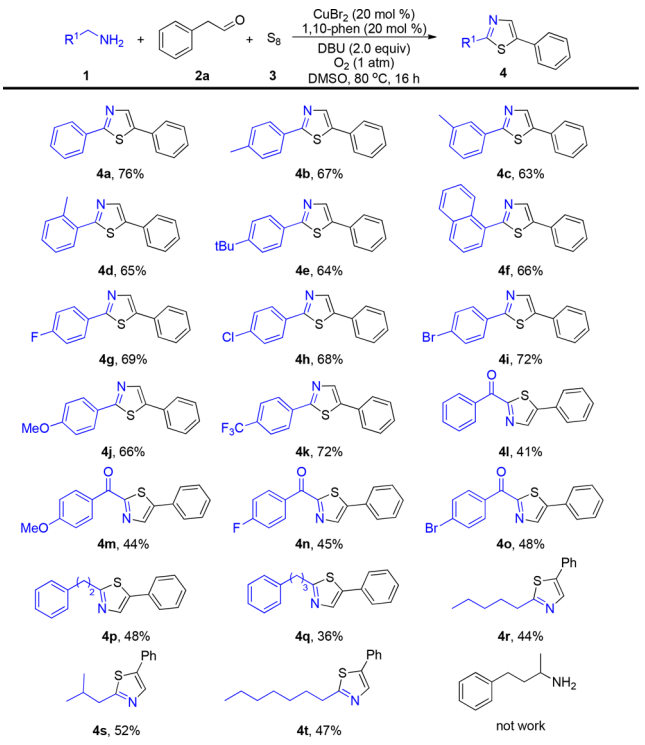
[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), **3** (0.16 mmol), $CuBr_2$ (20 mol %), 1,10-phen (20 mol %), DBU (2.0 equiv), and DMSO (3.0 mL), 16 h. [b]1.0 equiv of 1,10-phen was used.

catalysts, which further blocks the catalytic process and leads to the failure in synthesis of thiazoles. (2) An oxidant is required for this dehydrogenative annulation strategy.[7] Since the amine and aldehyde substrates are unstable under strong oxidative conditions, a weak oxidant, which does not cause the destruction of unstable substrates but can enable the dehydrogenative process, should be found in this protocol. Herein, by using the green and sustainable O_2 as the oxidant,[8] we report a novel Cu-catalyzed thiazole construction through multiple Csp^3−H sulfuration/annulations from readily available amines, aldehydes, and elemental sulfur (Scheme 1d).

Recently, we reported a copper-mediated oxazole synthesis via the oxygenation process with O_2, but 1.5 equiv of $CuBr_2$ is required for this transformation.[9a] With our constant endeavor in transition metal catalyzed aerobic oxidation and oxygenation reactions,[9] our initial efforts commenced with the reactions of benzylamine, acetaldehyde, and element sulfur utilizing $CuBr_2$ as catalyst in DMSO at 80 °C under air. Fortunately, the desired 2,5-diphenylthiazole **4a** was formed in 40% yield with only a trace amount of oxazole as the byproduct (Table 1, entry 1). Other copper salts were tested and exhibited similar or lower efficiencies (entries 2 and 3). Only a trace amount of product was obtained when the reaction was carried out in the presence of an acid additive (entry 4). In contrast, when an organic base DBU was added, diphenylthiazole was formed in 52% yield (entry 6). The reaction under dioxygen atmosphere afforded the product **4a** in 65% yield (entry 7). Notably, when 1,10-phen (1,10-phenanthroline) was employed as a ligand, the reaction performed well with 76% yield (entry 12). The reaction in the absence of a Cu catalyst did not work (Table 1, entry 14). These results demonstrate that this reaction undergoes a copper-catalyzed aerobic oxidative sulfuration/annulation process.

The scope of the reaction was then investigated by employing various substituted amines with phenylacetaldehyde (Scheme 2). It is noteworthy that the substituents at the phenyl ring, regardless of the electron-rich or electron-deficient nature, did not hinder the efficiency, producing the corresponding thiazoles in moderate to good yields. The position effect of substituents on the phenyl ring was investigated by using *p*-, *m*-, and *o*-substituted methyl benzylamines. The efficiency was unaffected with the formation of **4b**, **4c**, and **4d**, in 67%, 63%, and 65% yields, respectively. Naphthalen-1-yl methanamine showed good reactivity giving **4f** in 66% yield. In addition, fluoro-, chloro-, and bromo-substituted benzylamines produced the halo-substituted products **4g**−**4i** in good yields. Those products could be used for further coupling transformations as coupling partners.

Scheme 2. Construction of Thiazoles with Various Amines[a]



[a]Reaction conditions: **1** (0.3 mmol), **2a** (0.6 mmol), **3** (0.16 mmol), $CuBr_2$ (20 mol %), 1,10-phen (20 mol %), DBU (2.0 equiv), DMSO (3.0 mL), O_2 (1 atm), 16 h.

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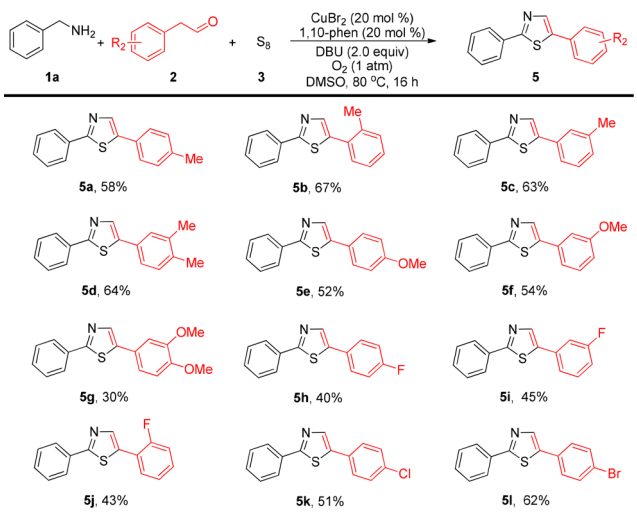
Notably, alkyl-substituted amines also proceeded well in this protocol, while the benzylic C−H bonds of phenethylamines were further oxidized into carbonyl groups in the corresponding products. For example, substituted phenethylamines worked well to produce the benzoyl thiazole derivatives **4l**−**4o** in moderate yields. Furthermore, the aliphatic amines also performed well leading to the corresponding alkyl-substituted thiazoles **4r**−**4t** in moderate yields. Unfortunately, α-methyl-substituted amine was not compatible in the present protocol.

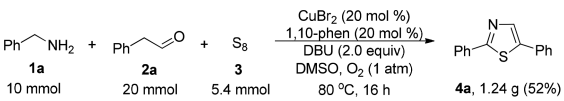
In subsequent studies, the applicability was further investigated by using various phenylacetaldehydes bearing different substituents on the aryl rings (Scheme 3). The

Scheme 3. Construction of Thiazoles with Different Aldehydes[a]



[a]Reaction conditions: **1a** (0.3 mmol), **2** (0.6 mmol), **3** (0.16 mmol), $CuBr_2$ (20 mol %), 1,10-phen (20 mol %), DBU (2.0 equiv), DMSO (3.0 mL), O_2 (1 atm), 16 h.

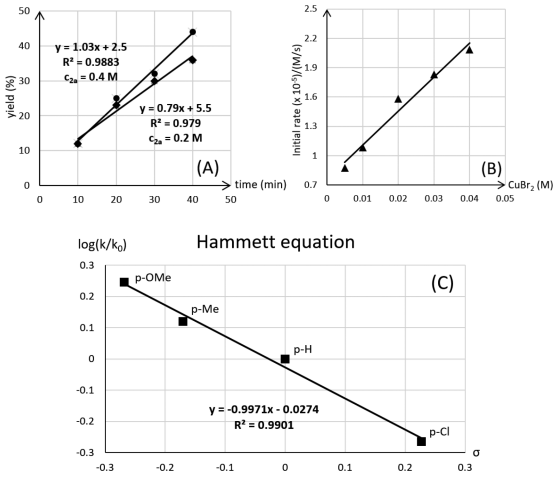
corresponding thiazole products **5a**−**5d** were produced in good yields (58%−67%). No significant position effect was observed. Phenylacetaldehydes bearing an electron-donating methoxy group produced **5e** and **5f** in yields of 52% and 54%, respectively. However, for 2-(3,4-dimethoxyphenyl)-acetaldehyde the yield of **5g** decreased to 30%. This substrate might be allergic to the oxidation system and degrade faster than forming the desired product. The fluoro-substituted phenylaldehydes were also tolerated in this protocol (**5h**−**5j**). In addition, 2-(4-chlorophenyl)acetaldehyde and 2-(4-bromophenyl)-acetaldehyde worked well producing **5k** and **5l** in 51% and 62% yields, respectively. Moreover, this protocol was applied to gram-scale reaction with the formation of **4a** in 52% yield (eq 1).



(1)

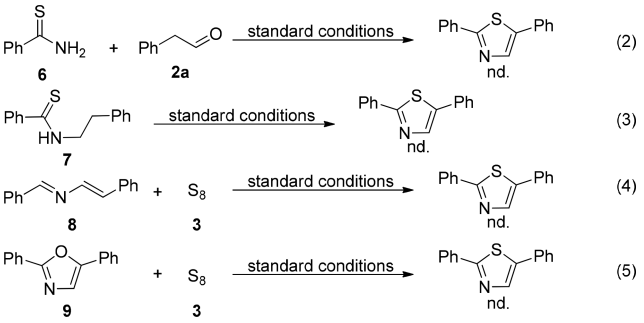
Furthermore, the kinetic study of this process was studied with the model reaction of **1a** and **2a** (Scheme 4). The effect of concentration on phenylacetaldehyde was tested by utilizing 0.2 and 0.4 M **2a**. The reaction rate rises together with the concentration of **2a** (Scheme 4A). The increasing concentration might promote a dehydration process between anilines and aldehydes in forming an imine intermediate. When the

Scheme 4. Kinetic Study



concentration of $CuBr_2$ was tested, a first-order dependence was established (Scheme 4B). This result suggested that in this reaction the copper catalyst might be the catalytically active species.[10] For further understanding of this process, different *p*-substituted benzylamine derivatives were utilized to establish a Hammett equation. We were pleased to find a linear relationship between different electron-withdrawing groups and electron-donating groups (Scheme 4C). This plot of Hammett equation is linear with a negative slope. In this process, the electron-donating groups accelerated the reaction. The reason for this phenomenon is probably due to the oxidative activity of the Csp^3−H bonds in electron-rich benzylamines.

Moreover, some control experiments were conducted to interpret the reaction pathway. The reaction of benzothioamide **6** and 2-phenylacetaldehyde **2a** did not give the desired thiazole product under the standard conditions (eq 2). *N*-Phenethyl-



benzothioamide **7** did not work either (eq 3). The 1,4-diphenyl-2-azabutadiene **8** was prepared, but it did not react with element sulfur under the standard conditions (eq 4). In addition, the atom exchange between oxygen and the sulfur atom was not detected in 2,5-diphenyloxazole **9** (eq 5). Those results demonstrate that the compounds **6**−**9** are not the intermediates involved in this transformation.

Although the detailed mechanism is not completely clear yet, a plausible mechanism is outlined in Scheme 5 on the basis of the above results and previous reports.[2j,5a] Initially, the condensation of anilines and aldehydes yields imines **A**[11] and **B** with the tautomerization. Then intermediate **B** reacts with an electrophilic element sulfur to form species **C**.[12] Afterward, further aerobic oxidation assisted by Cu catalysis would produce **D**. Elimination of element sulfur and the intra-

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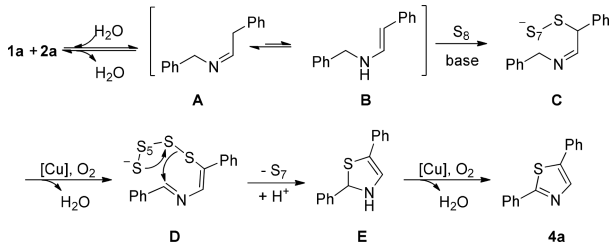
Scheme 5. Proposed Mechanism



molecular nucleophilic addition of intermediate **D** generate intermediate **E**,[13] which undergoes a further oxidative process under the Cu catalysis and affords the target molecule **4a**.

In summary, we developed a novel Cu-catalyzed aerobic oxidative approach to thiazoles. Simple aldehydes, amines, and element sulfur were employed to construct thiazoles for the first time by this protocol through a novel multiple Csp^3–H bond cleavage process. The substrate scope is broad with the tolerance of aliphatic amines. Inexpensive Cu catalysts, commercially available substrates, and green oxidants were used, which makes this protocol economical, step-efficient, and environmentally friendly. Further studies on the bioactivity screening of these products are ongoing with the collaborators.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00840.

Experimental procedures, full characterization of products, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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