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COMMUNICATION

Dioxygen-Triggered Oxidative Cleavage of C-S Bond towards C-N Bond Formation

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The research on the cleavage of C-C bond has been well developed. By comparision with this, the activation of C-S bond remains challenging. Herein, dioxygen-triggered oxidative cleavage of C-S bond has been achieved, delivering a series of N-containing heterocyclic compounds which are frequently found in pesticides and pharmaceuticals. Additionally, the potential ultility of this protocol was further demonstrated by gram-scale experiment. Mechanistically, dioxygen plays a key role in the cleavage of C-S bond towards C-N bond formation.

The highly discriminating activation and transformation of an inert chemical bond are among the most important processes throughout the chemistry. To date, transition-metal-catalyzed the C–C bond cleavage have been well developed.[1] In contrast, the development of the cleavage of C–S bond, which are important structural motifs in natural products, is relatively late.[2] Over the past several decades, with more and more attention in the cross-coupling reaction, the C–S bond cleavage and transformation have been explored from the standpoint of diverse synthetic, catalytic, bioorganic, bioinorganic, and theoretical chemistry.[3] Thus, organosulfur compounds have shown increasing importance in the construction of new chemical bonds as coupling partners or building blocks.[4]

In this section of C–S bond activation, the most developed one is the C–S bond insertion by a transition-metal, such as palladium, ruthenium, rhodium, iridium, etc.[5] Meanwhile, the generation of a sulfur radical via the C–S bond homolytic cleavage, also has been developed.[6] Although many methods for the C-S bond cleavage are known,[7] its efficient application is still limited owing to the relative sluggishness of the C–S bond.[8] Thus, seeking an efficient approach to facilitating activation of C-S bond is valuable yet difficult.

Thiazoles are important groups of heterocyclic compounds due to their drug utility,[9] and a number of biologically and physiologically active compounds with bactericidal, fungicidal, tuberculostatic, and anti-inflammatory properties have been synthesized based on them.[10] Among, benzothiazoles with a nitrogen substituent have frequently been used as core structures for the development of pharmaceutical reagents.[11] Considering the synthetic value, developing mild and sustainable strategies for the production of various nitrogen-containing heterocyclic compounds is worthwhile. The substitutions of 2-halobenzothiazoles or 2-thiobenzothiazoles with amine have been successfully developed to provide 2-N-substituted benzothiazoles, which usually require several steps or have a limitation of substrate scope.[12] Additionally, several approaches based on metal catalysis have also been developed. Remarkable works have been focused on the use of copper[11,13], palladium[14], silver[15], nickel[16], cobalt and manganese[17] as the metal catalyst to offer the 2-N-substituted benzothiazoles with the requisite substrates of 2-halobenzothioureas, benzothiazoles, N-aryl thioureas, isocyanide, 2-iodobenzamine, and activated (hetero)aryl chlorides etc. Despite great success had been made, an approach with broad functional group tolerance to generating nitrogen-containing heterocyclic compounds was necessary yet challenging.[11-18]

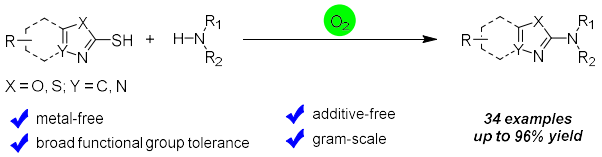

Fig. 1 The formation of N-substituted azoles.

Environmental concerns prompted us to seek more environmentally friendly and practical method for the molecule synthesis. As we all know, dioxygen, an attractive alternative of oxidants, is environmentally friendly, non-toxic and economic. Based on our previous research,[19] we speculated that the N-substituted aromatic heterocycle compounds might be furnished through the C-S bond cleavage of aromatic

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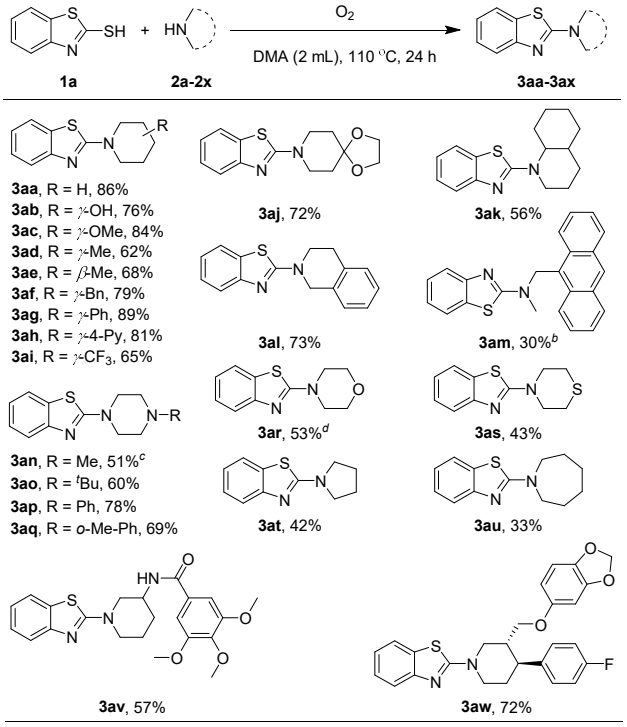
mercaptans by using dioxygen as a mediator. Herein, we describe a practical and sustainable protocol for the synthesis of N-substituted aromatic heterocycle compounds through dioxygen-triggered cleavage of C-S Bond process, which not only offers a series of N-substituted aromatic heterocycle compounds with good efficiency, but also provides an interesting strategy for the C-S bond activation (Fig. 1).

At the outset of this study, we attempted to investigate the oxidative cleavage of C-S bond towards C-N bond formation by using 2-mercaptobenzothiazole **1a** and piperidine **2a** as the model substrates under the dioxygen atmosphere. When employing iodine as an additive, the reaction of **1a** (0.3 mmol) and **2a** (0.9 mmol) was carried out in *N,N*-dimethylacetamide (DMA) (2.0 mL) at various temperatures for 12 h (Table S1, entries 1-4). Pleasingly, the desired product **3aa** can be obtained in the higher GC yield of 55% at 110 °C (Table S1, entry 3). When the other solvents such as dimethyl sulfoxide (DMSO), *N,N*-dimethylformamide (DMF) and *N*-methyl pyrrolidone (NMP) were used in the transformation, the yields of **3aa** were decreased, demonstrating that DMA was an optimal solvent for the reaction (Table S1, entries 5-7). Compared with ammonium chloride (NH_4Cl), sodium acetate (NaOAc), and triethylamine (Et_3N), it was interesting that no additive was more suitable to promote the formation (Table S1, entries 8-11). Then, the yield wasn't significantly improved while the reaction time was lengthened to 24 h (Table S1, entry 12). However, it was noteworthy that **3aa** could be obtained in 94% GC yield by using DMA as the solvent with 4 equivalent **2a** at 110 °C under O_2 for 24 h (Table S1, entry 13). Subsequently, the increase or decrease of the reaction time were unfavorable (Table S1, entries 14-16). Moreover, the yields of **3aa** fell sharply when the reactions were carried out under air or N_2 instead of O_2 (Table S1, entries 17-18). These results revealed that O_2 played an essential role in this transformation.

With the optimal condition in hand, various kinds of N-substituted aromatic heterocycle compounds were furnished in moderate to high yields by this oxidative cleavage of C-S bond towards C-N bond formation method under dioxygen (Table 1). First, we extended the scope of piperidines with respect to both electron-donating and electron-withdrawing substituents. Not only *γ*-hydroxyl-piperidine but also *γ*-methoxyl-piperidine were the compatible substrates and reacted smoothly to give the desired products (**3ab** and **3ac**). As for *γ*- and *β*-methyl-substituted piperidines, the moderate yields of 62% and 68% were achieved, respectively (**3ad** and **3ae**). Subsequently, piperidines substituted on the *γ*-position of nitrogen atom, such as *γ*-benzyl-piperidine and *γ*-phenyl-piperidine, showed the satisfactory reactivity (**3af** and **3ag**). Additionally, the good yields were obtained when functional *γ*-substituted piperidines with electron-withdrawing groups were studied. For example, *γ*-4-pyridyl-piperidine and *γ*-trifluoromethyl-piperidine were compliant substrates and afforded 81% and 65% yields, respectively (**3ah** and **3ai**). Furthermore, 4-piperidone ethylene ketal **2j** afforded 72% yield and decahydroquinoline **2k** afforded 56% yield. Notably, 1,2,3,4-tetrahydroisoquinoline was the compatible substrate and gave rise to the corresponding product in 73% yield (**3al**). Besides, 1-(anthracen-9-yl)-N-methylmethanamine, the alkyl secondary amine, did not hinder the formation of product (**3am**). Unfortunately, we failed to extended the substrate scope to alkyl primary amine and arylamines. In the case of the *N*-alkyl piperazines with different substitutions on both the aliphatic and aromatic portions, moderate yields were achieved (**3an**, **3ao**, **3ap** and **3aq**). In addition, morpholine **2r** and thiomorpholine **2s** were also tolerated as the substrates for the functionalization of C-N bond, yielding the corresponding products in 53% and 43%, respectively (**3ar** and **3as**). For five-membered and seven-membered cyclic amines, such as pyrrolidine **2t** and hexamethyleneimine **2u**, were all tolerated under the same condition, providing the chance for further chemical transformation (**3at** and **3au**). Last but not least, the pharmaceutical molecules containing N-atom such as troxipide and paroxetine delivered moderate to good yields (**3av** and **3aw**).

Then we turned our attention toward the effect of various aromatic mercaptans on the oxidative cleavage of C-S bond towards C-N bond formation (Table 2). The introductions of halogen atom such as Cl and Br on the phenyl ring of 2-mercaptobenzothiazole were all tolerated well, providing the desired products in 61% and 46% yield, respectively (**3ba** and **3ca**). Upon using 2-mercapto-6-nitrobenzothiazole **1d**, the corresponding product could also be readily prepared (**3da**). 2-mercaptobenzoxazoles bearing not only electron-withdrawing

Table 1. The scope of amines under dioxygen-triggered oxidative conditions[a]



[a] Conditions: **1a** (0.3 mmol), **2** (1.2 mmol) in DMA (2.0 mL) under a dioxygen atmosphere at 110 °C for 24 h, isolated yields. [b] The reaction was conducted at 90 °C. [c] The reaction was conducted at 100 °C. [d] The reaction was conducted for 36 h.

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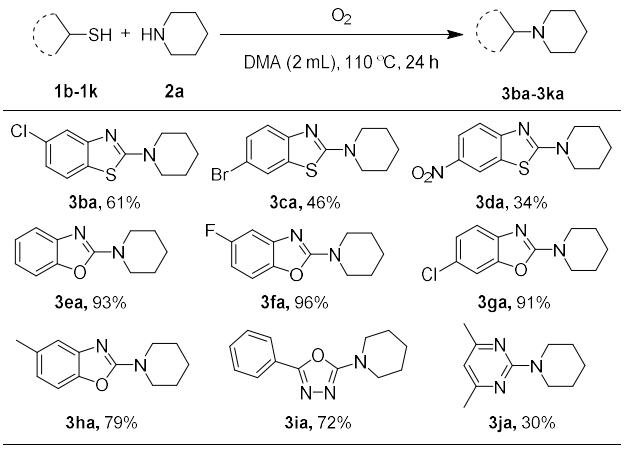
groups, such as F and Cl, but also electron-donating groups, such as methyl, could react smoothly with **2a** to give the desired

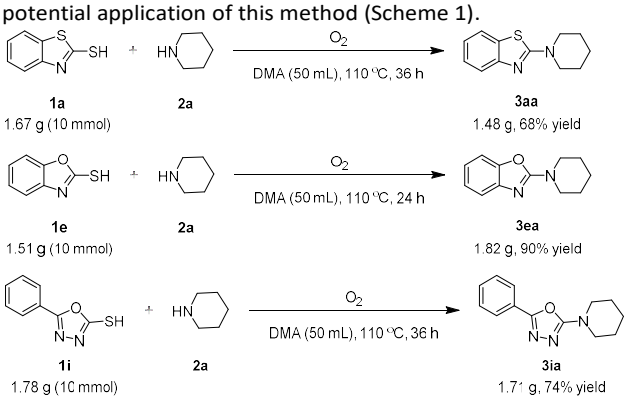
Table 2. The scope of aromatic mercaptans under dioxygen-triggered oxidative conditions [a]



[a] Conditions: **1** (0.3 mmol), **2a** (1.2 mmol) in DMA (2.0 mL) under a dioxygen atmosphere at 110 °C for 24 h, isolated yields.

products in 79–96% yields (**3ea**, **3fa**, **3ga** and **3ha**). Importantly, 1,3,4-oxadiazole-2-thiol derivative such as 5-phenyl-1,3,4-oxadiazole-2-thiol proceeded in 72% yield as well (**3ia**). Pleasingly, 4,6-dimethyl-2-mercaptopyrimidine was able as well to give the expected product (**3ja**).

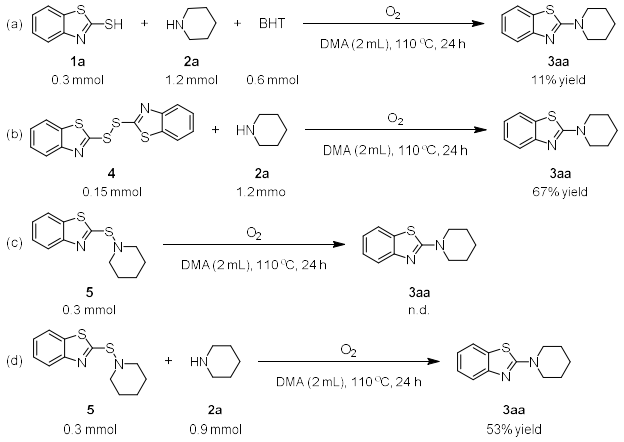
To demonstrate the utility of this C-N bond formation, the efficiency of this method on the larger scale synthesis was investigated. Delightfully, it was noteworthy that this procedure could be scaled up to gram quantities of the desired 2-piperidinobenzothiazole, 2-piperidinobenzooxazole and 2-phenyl-5-piperidino-1,3,4-oxadiazole with the same level of yields as that of the small scale reaction. For instance, 1.48 g of **3aa**, 1.82 g of **3ea** and 1.71 g of **3ia** could be isolated in the comparable yields of 68%, 90% and 74%, highlighting the potential application of this method (Scheme 1).



Scheme 1. The gram-scale reactions.

To know more details about the mechanism of this protocol, a series of mechanistic experiments were performed. Given that activation of O_2 mostly involves a radical pathway, radical-trapping experiment was firstly carried out. When the well-known radical scavenger 2,6-di-tert-butyl-4-methylphenol (BHT, 2 equivalent) was added to the standard reaction system, the conversion was significantly suppressed and only 11% yield was obtained (Scheme 2a), thus revealing that this process may proceed through a radical pathway.

Subsequently, the intermediate experiments were also performed (Scheme 2). 2,2'-Dithiobis(benzothiazole) **4** reacted with **2a** under the standard condition to give **3aa** in 67% yield, suggesting **4** might be the intermediate in this transformation. Furthermore, 2-(piperidin-1-ylthio)benzothiazole **5**, which was detected by GC-MS in the reaction, did not afford the desired product **3aa** under the standard condition without **2a**. In contrast, **5** might be the vital reaction intermediate for the C-N bond formation, because of a 53% yield of **3aa** was obtained under the standard condition with 3 equivalent of **2a**.



Scheme 2. The controlled experiments.

According to the previous reports[19,20] and the above results of mechanistic studies, a plausible pathway for this reaction was proposed (Fig. 2). Initially, the intermediate **4** was generated from autoxidation of **1a**. Then, a intermolecular substitution reaction between **4** and **2a** afforded intermediate **5** with the release of **1a**. **2a** was oxidized by O_2, generating radical **I**. Then, radical addition of **I** to **5** afforded the desired product **3aa** and di(piperidin-1-yl)sulfane **II** which was detected by GC-MS.

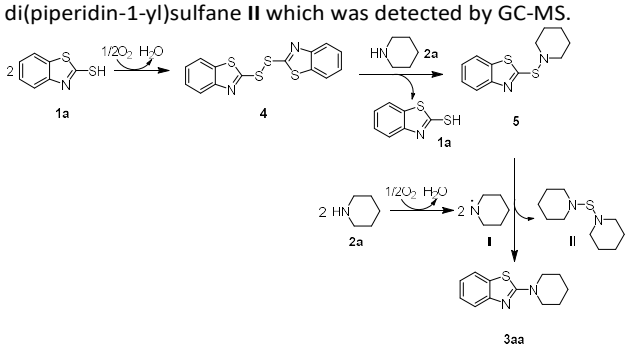


Fig. 2 Proposed mechanism.

In summary, we have successfully developed a practical strategy for the construction of C-N bond from readily available starting materials through dioxygen-triggered oxidation cleavage of C-S bond. This reaction features simple operation and gram-scale synthesis. Crucially, neither metal catalyst nor

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additional additive is necessary in these transformations. Mechanistic investigations demonstrate that the S-N bond compound might be the vital intermediate for the C-N bond formation. Ongoing research, including further mechanistic details and expanding the substrate scope, are currently underway.

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Conflicts of interest

There are no conflicts to declare.

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