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Copper-Catalyzed Oxidative Thioamination of Maleimides with Amines and Bunte Salts

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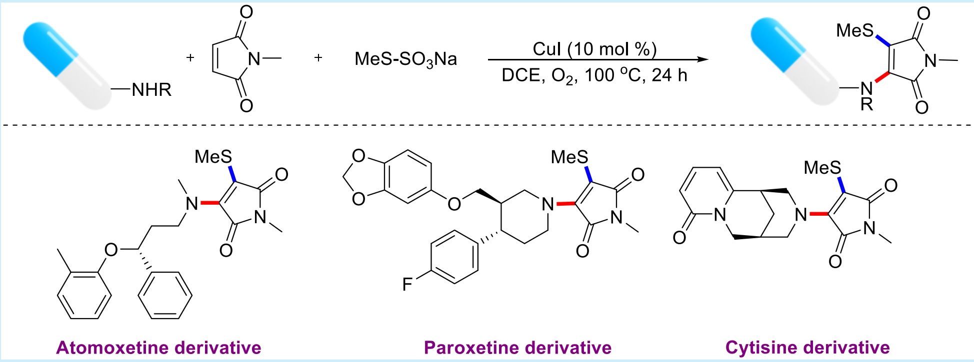

ABSTRACT: Herein, we describe the first example of copper-catalyzed oxidative thioamination of maleimides with secondary amines and Bunte salts with the achievement of C−N and C−S bonds in a single flask. The protocol showcases a prominently broad substrate scope and is also efficient for the late-stage modification of an array of pharmaceuticals. Preliminary mechanistic investigation indicates copper-catalyzed oxidative amination of maleimides with amines to form reactive enaminone and subsequent intermolecular alkenyl C−H thiolation.

Transition-metal catalyzed vinylic C−H thiolation is one of the most efficient protocols to synthesize the vinyl sulfides by the formation of a new C−S bond.[1] Although a variety of methodologies have been made on this avenue, the sulfurating reagents typically employed are limited to narrow-ranged diaryl disulfides, ArSO$_2$Cl, and rotten alkyl thiols. Thus, it would dramatically limit their potential applications for late-stage modification of bioactive molecules for novel drug research and development. In contrast, the use of Bunte salts would be a promising sulfur source in view of its structural diversity, stability, and no odor.[2] As far as we are aware, there has been no report on such a transformation to construct the structural diverse vinyl thioethers. In continuation of our studies on alkene functionalization,[3] herein we describe the development of copper-catalyzed oxidative thioamination of electron-deficient alkenes with amines and S-alkyl Bunte salts with the formation of C−N and C−S bonds in a single flask.

In recent years, the oxidative coupling of Bunte salts with a carbon nucleophile has received increasing attention. Jiang's group demonstrated the sulfuration of boronic acids using copper-catalyzed oxidative coupling under CO$_2$ atmosphere.[4] Aryltriethoxysilane could also be converted into thioether and thioester with a ligand-controlled strategy by the same group.[5] In addition, Yi's group also developed an efficient copper-catalyzed decarboxylative sulfuration of alkynyl carboxylic acids with Bunte salts.[6] However, oxidative coupling of electron-deficient alkenes with Bunte salts has never been reported, because these two coupling partners easily occur in classical thia-Michael addition[7] (Scheme 1A). Ideally, if one common chemical could be introduced in electron-deficient alkenes and endowed with new reactivity to achieve a multicomponent reaction, it would advance synthetic innovation and novel drug research. Therefore, we envisioned developing a copper-catalyzed three-component coupling with maleimides, Bunte salts, and amines (Scheme 1B). As part of our design, we assumed that copper-catalyzed oxidative amination of maleimides with amines to generate enaminone, in this case, the electrophilic reactivity of maleimides could be transformed into potent nucleophilicity owing to the strong electron-donating of an amino group. Then, the intermolecular oxidative cross-coupling of this key intermediate with Bunte salts provides a promising route to construct more structurally diverse thiolated enaminone compounds. As a result, this transformation not only establishes an efficient protocol to access thioaminationed maleimides via C−N bond and C−S bond formation but also provides a complementary protocol

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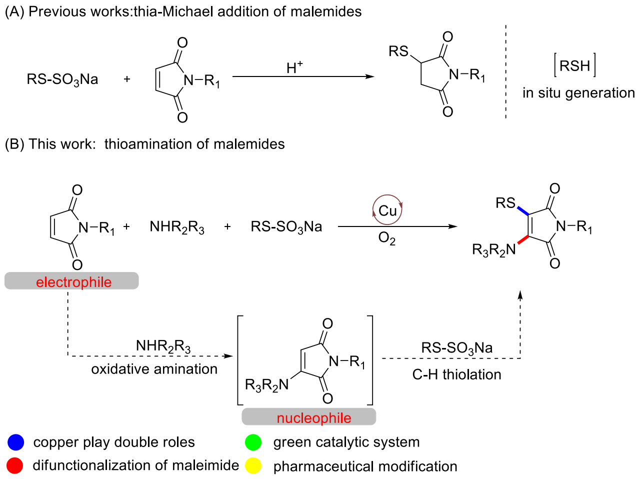
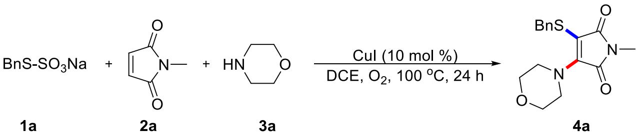
Scheme 1. Copper-Catalyzed Thioamination of Maleimides via Umpolung Strategy



for existing three-component acetamidosulfenylation of alkenes with Bunte salts and nitriles.

At the outset of our study, we chose sodium S-benzyl sulfurothioate **1a**, *N*-methyl maleimide **2a**, and morpholine **3a** as the model substrate to test the feasibility of copper-catalyzed thioamination of electron-deficient alkenes. After thorough optimization of reaction conditions, the reaction was conducted using CuI as the catalyst, DCE as the solvent, and oxygen as the green oxidant at 100 °C, the desired product **4a** was isolated in 83% yield (Table 1, entry 1). It was noteworthy that sulfenylation of maleimides,[8] thia-Michael addition of Bunte salt with maleimides,[7] and α-amination of Bunte salt with amines[9] were not observed at all during optimization of the reaction conditions. It was found that the choice of copper catalyst was a critical success factor for this reaction. The results suggest that only CuI could provide the corresponding product; other copper salts were completely ineffective (entries 2–4). Furthermore, the addition of a base inhibited the transformation and the addition of an acid decreased the yield of **4a** to 65% (entries 5 and 6). In addition, the current reaction was very sensitive to solvent; polar, weak coordination, and apolar solvents were undesirable (entries 7–9). When Ag_2CO_3 was used as the oxidant, although *N*-methyl maleimide was fully consumed, **4a** was generated in a trace amount (entry 10). The effect of ligand was next assessed, and the addition of Phen was detrimental to reaction efficiency (entry 11). Finally, control experiments demonstrated that a copper catalyst and oxygen played essential roles in promoting the three-component tandem reaction (entries 12–13).

Table 1. Reaction Optimization[a]

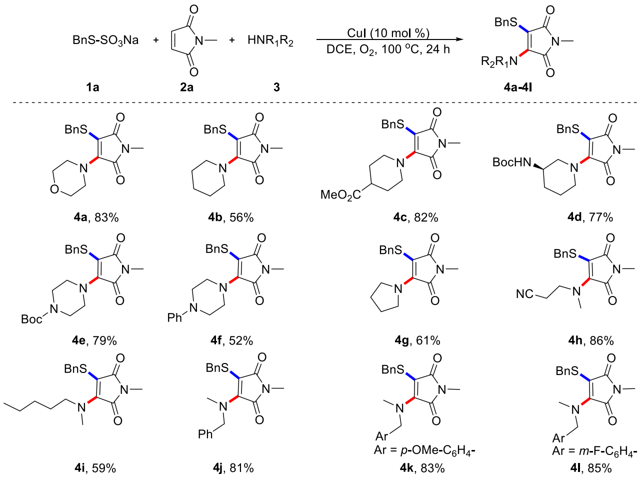


entry	variation	yield (%)[b]
1	none	83
2	$CuCl_2$ instead of CuI	0
3	$CuBr_2$ instead of CuI	0
4	$Cu(OAc)_2$ instead of CuI	0
5	Na_2CO_3 (0.4 mmol) as additive	0
6	TsOH (0.4 mmol) as additive	65
7	DMSO instead of DCE	0
8	CH_3CN instead of DCE	0
9	Toluene instead of DCE	0
10	Ag_2CO_3 (0.4 mmol) as oxidant	trace
11	Phen (0.02 mmol) as additive	44
12	Under N_2	0
13	No CuI	0

[a]Reaction conditions unless specified otherwise: **1a** (0.4 mmol), **2a** (0.2 mmol), **3a** (0.4 mmol), CuI (0.02 mmol), DCE (2.0 mL), under O_2, 100 °C, 24 h. [b]Isolated yield.

With the optimized reaction conditions in hand, we examined the scope of amines in the copper-catalyzed three-component tandem reaction. As shown in Scheme 2, a wide range of cyclic secondary amines could smoothly undergo this transformation. Morpholine (**4a**), piperidine (**4b–4d**), piperazine (**4e–4f**), and pyrrolidine (**4g**) were suitable substrates, and the corresponding products were obtained in moderate to good yields. This reaction showcases good functional group tolerance, including ester, Boc, phenyl, alkyl, cyano, methoxyl, and fluoro, thus providing a useful building block for further transformation of the desired products. Moreover, acyclic secondary amines (**4h** and **4i**) are also amenable to vinylthiolation, indicating the versatility and compatibility of the current catalytic system. In addition, this method was viable to *N*-methyl benzylamine substrates (**4j–4l**), giving the vinylthiolated products in good yield. However, when primary alkyl amines, anilines, and amides were used as coupling partners, no thioaminated product was detected, probably owing to the poor nucleophilicity of the starting material.

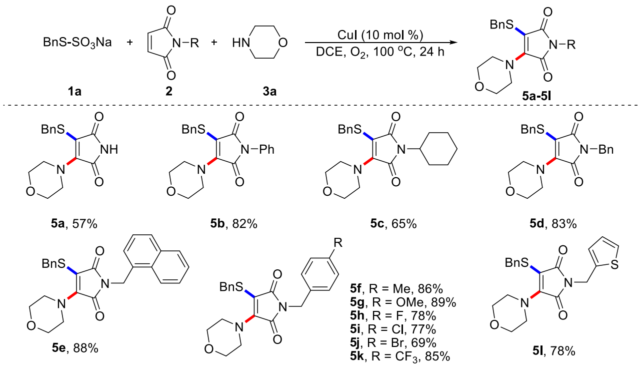
Scheme 2. Secondary Amines Scope[a]



[a]Reaction conditions: Tabel 1, entry 1. Isolated yields after column chromatography are given.

Next, we focused our attention on testing the feasibility of structurally diverse maleimides reacting under the robust reaction conditions (Scheme 3). The copper-catalyzed oxidative thioamination of a variety of maleimides (**2a–2l**) exhibited versatility and extensibility, and the predicted products (**5a–5l**) were generated in good to excellent yields. Especially, it was found that free maleimide (**5a**) also exhibited high reactivity and afforded the corresponding product in synthetically useful yield. More generally, *N*-substituted maleimides were efficiently thioaminated to give the

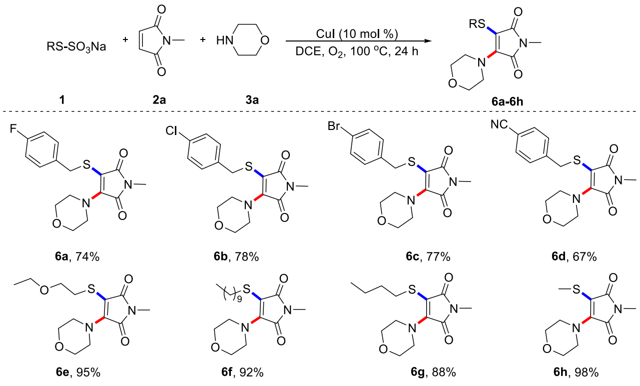
Scheme 3. Maleimides Scope[a]



[a]Reaction conditions: Tabel 1, entry 1. Isolated yields after column chromatography are given.

corresponding products in good yields. Furthermore, many synthetically important functional groups on the benzene ring of *N*-aryl maleimides, including methyl (**5f**), methoxy (**5g**), halogen moiety (**5h**−**5j**), and trifluoromethyl (**5k**), were well tolerated; these target products could be further modified via well-developed cross-coupling methodology. To our delight, maleimide bearing thiophene also reacted smoothly with **1a** and **3a** to afford the desired product **5l** in 72% yield.

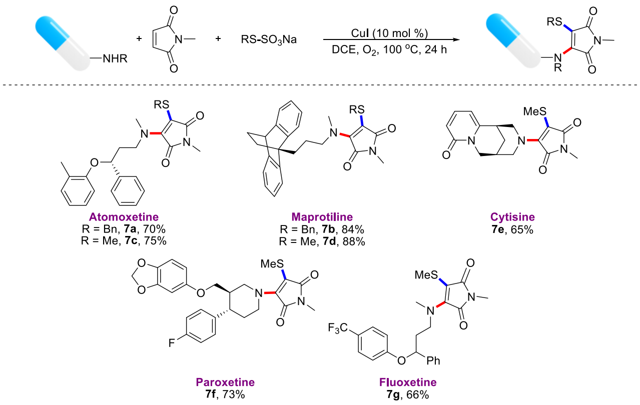
Scheme 4. Bunte Salts Scope[a]



[a]Reaction conditions: Tabel 1, entry 1. Isolated yields after column chromatography are given.

Selected examples of the thioaminated maleimides synthesis are illustrated in Scheme 4. The current strategy could be applicable to an array of functionalized S-alkyl Bunte salts under the optimal reaction conditions, giving the expected products in satisfactory yields. Alkyl substituted Bunte salts displayed more reactivity than benzyl substituted ones, probably due to less steric repulsion between the thiol and amino groups. It is worth mentioning that sodium S-methyl sulfurothioate also could be utilized as a methylthio source in the current three-component reaction and the vinyl methyl sulfide (**6h**) was obtained in excellent yield.

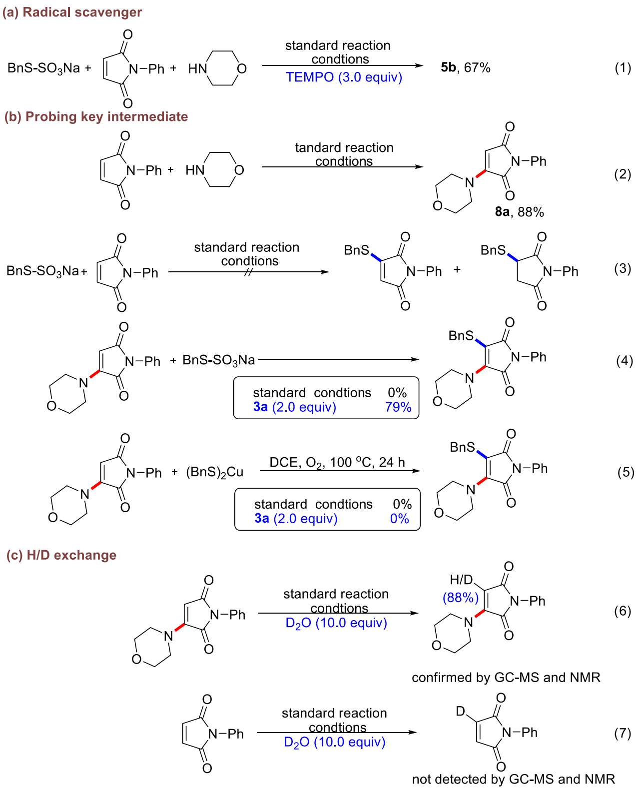
Scheme 5. Late-Stage Modification of Pharmaceuticals



Late-stage modification of pharmaceuticals has been become one of the most efficient gateways for novel compound discovery and development. As shown in Scheme 5, the current strategy provides practical evidence for the late-stage vinylthiolation of secondary amine-containing pharmaceuticals. Atomoxetine[10] (**7a** and **7c**) (marketed as Strattera), a drug used for treating attention-deficit/hyperactivity disorder, could be readily vinylthiolated with high efficiency. The application of this protocol was demonstrated on Maprotiline[11] (**7b** and **7d**), which inhibits neuronal norepinephrine reuptake. The highly efficient synthesis of thioaminated Cytisine **7e**, a drug more affordable in smoking cessation treatment than nicotine, was also achieved.[12] Meanwhile, common antidepressant drugs Paroxetine[13] (**7f**) and Fluoxetine[14] (**7g**) were amenable coupling partners under the current reaction conditions.

Given the versatility of copper-catalyzed thioamination of maleimides, we conducted some mechanistic investigations to shed substantial light on the sequence of three-component coupling (Scheme 6). First, maleimide difunctionalization was performed in the presence of a frequently used radical inhibitor affording the expected product with only a minor loss in efficiency (eq 1), which suggested a radical-based mechanism could be excluded. Second, when the *N*-phenyl maleimide and

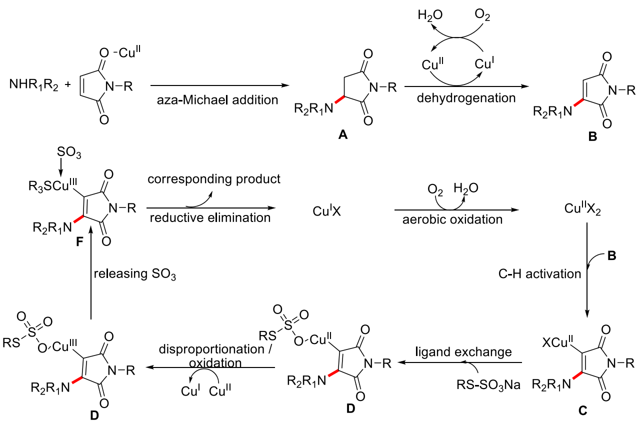
Scheme 6. Preliminary Mechanism Investigation



morpholine were subjected to standard reaction conditions, the oxidative amination product was obtained in 88% yield (eq 2); in comparison, the treatment of maleimide with Bunte salt did not afford thia-Michael addition and oxidative sulfuration products (eq 3). To further elucidate the sulfuration of enaminone, the reaction between **1a** and **8a** was also performed, however no desired product was detected. Interestingly, after the addition of some amount of morpholine, **4a** was dramatically generated in 79% yield (eq 4). This result clearly indicates the amine not only acts as a substrate in the multicomponent reaction but also functions as an activator of Bunte salt to promote the enaminone C−H sulfuration. To examine whether the enaminone **8a** is traped by thiolcopper species, we prepared a $(BnS)_2Cu$ complex[15] and reacted it with **8a** under optimal reaction condition, in both the absence and presence of an amine. The anticipated product was not observed, which means thiolcopper was not a key intermediate under the current reaction system. Finally, 88% deuterium incorporation of enaminone **8a** was confirmed in the presence of D_2O under the standard reaction conditions. In contrast, no H/D exchange product of simple maleimides was detected by NMR and GC-MS.[16] These results imply that reversibility of enaminone C−H activation under the current catalytic system probably may be ascribed to the strong electron-donating property of the amino group.

On the basis of experimental findings and previous literature, a plausible reaction mechanism for copper-catalyzed thioamination of maleimides is proposed in Scheme 7. First, copper-catalyzed oxidative amination of maleimides with secondary amines form ksey intermediate **B** via aza-Michael addition/oxidative dehydrogenation steps.[17] Afterward, the reaction of the Cu(II) salt with **B** generates vinylcopper complex **C** via C−H activation,[18] with subsequent ligand exchange between **D** and S-alkyl Bunte salt. Disproportionation of **D** with Cu(II) forms **E**,[19] which finally undergoes reductive elimination to afford the corresponding product with the release of SO_3.[20] It should be noted that the copper salt played at least three roles in the whole reaction process.

Scheme 7. Proposed Mechanism



In summary, we have developed a general and efficient method of copper-catalyzed thioamination of maleimides with S-alkyl Bunte salts and secondary amines. The significant features of this tandem reaction include the use of almost no odor S-alkyl Bunte salts as the alkylthiol reagent, a simple catalytic system, a green oxidant, and excellent functional group tolerance. Preliminary mechanism studies reveal that the introduction of an amino group into the skeleton of maleimides would endow new reactivity. This approach is amenable to the late-stage vinylthiolation of secondary amine-containing pharmaceuticals, which would accelerate the discovery of new novel drugs. This reaction not only opens a new door for the synthetic application of S-alkyl Bunte salts as a sulfuration reagent but also offers new insight into the oxidative difunctionalization of electron-deficient alkenes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00207.

^{1}H and ^{13}C NMR spectra of all new compounds and the experimental procedures (PDF)

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Notes

The authors declare no competing financial interest.

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