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Three-Component Coupling Reactions of Maleimides, Thiols, and Amines: One-Step Construction of 3,4-Heteroatom-functionalized Maleimides by Copper-Catalyzed C(sp^2)–H Thioamination

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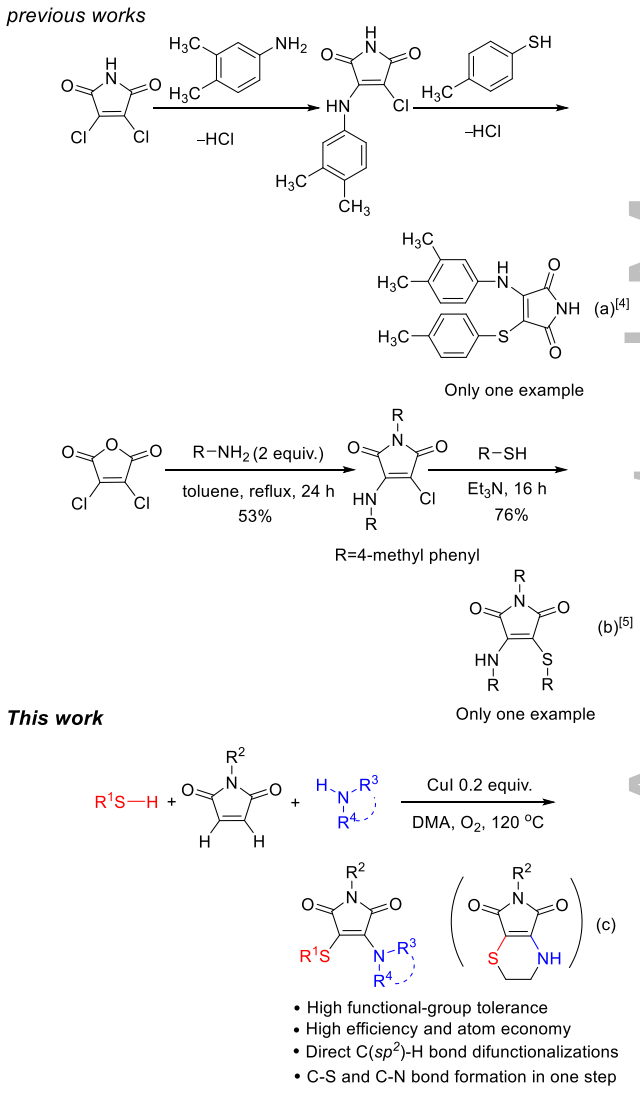
Abstract: A copper-catalyzed intermolecular thioamination of maleimides with thiols and amines has been developed. A diverse range of 3-amino-4-thiomaleimides and 3,4-dihydropyrrolo[3,4-*b*][1,4]thiazine-5,7(2*H*,6*H*)-diones were obtained with good yields, involving C–N and C–S bond formations. This methodology is very practical and features high atom economy, excellent functional group tolerance.

Keywords: copper catalysis; thioamination; maleimides; thiols; amines

Maleimides are ubiquitous structural motifs found in a multitude of natural products and drug candidates as well as functional materials.[1] Additionally, they could be transformed into diverse, important heterocyclic frameworks such as succinimides, pyrrolidines, lactims, and γ-lactams.[2] Thus, a great deal of attention has been focused on the development of new synthetic routes to access functionalized maleimides.[3] 3-amino-4-thiomaleimides are particularly important organic molecules due to their antibacterial and antitumor activities.[4] Traditionally, they have been synthesized from the sequential nucleophilic substitution of 3,4-dichloromaleimides with anilines and benzenethiols (Scheme 1a).[4a] Moreover, the 3,4-dichloromaleic anhydrides have also served as substrates to build 3-amino-4-thiomaleimides in two steps, albeit with low yield (Scheme 1b).[5] However, these methods require the application of reactive prefunctionalized materials and multistep reactions. Hence, the development of novel and practical methods for one-step synthesis of 3-amino-4-thiomaleimides using nonfunctionalized reagents remains both a considerable challenge and a most useful addition to this branch of chemistry.



Scheme 1. Copper-catalyzed intermolecular thioamination of maleimides.

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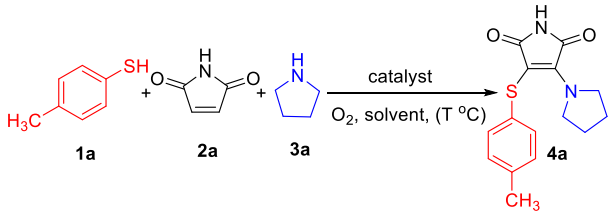
Table 1. Optimization of the reaction conditions.[a]



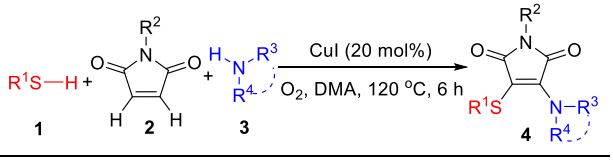
Entry	Catalyst (equiv.)	Solvent	Temp. (℃)	Yield [%][b]
1[c]	CuCl (1.0)	DMSO	120	37
2	CuCl (1.0)	DMSO	120	52
3	CuBr (1.0)	DMSO	120	58
4	CuI (1.0)	DMSO	120	73
5	$CuCl_2$ (1.0)	DMSO	120	36
6	$Cu(OAc)_2$ (1.0)	DMSO	120	45
7	I_2 (1.0)	DMSO	120	27
8	CuI (1.0)	DMA	120	78
9	CuI (1.0)	MCB	120	18
10	CuI (1.0)	DMF	120	67
11	CuI (1.0)	Dioxane	reflux	25
12	CuI (0.5)	DMA	120	82
13	CuI (0.2)	DMA	120	85
14	CuI (0.1)	DMA	120	57
15	CuI (0.2)	DMA	100	67
16	CuI (0.2)	DMA	140	71
17	—	DMA	120	0

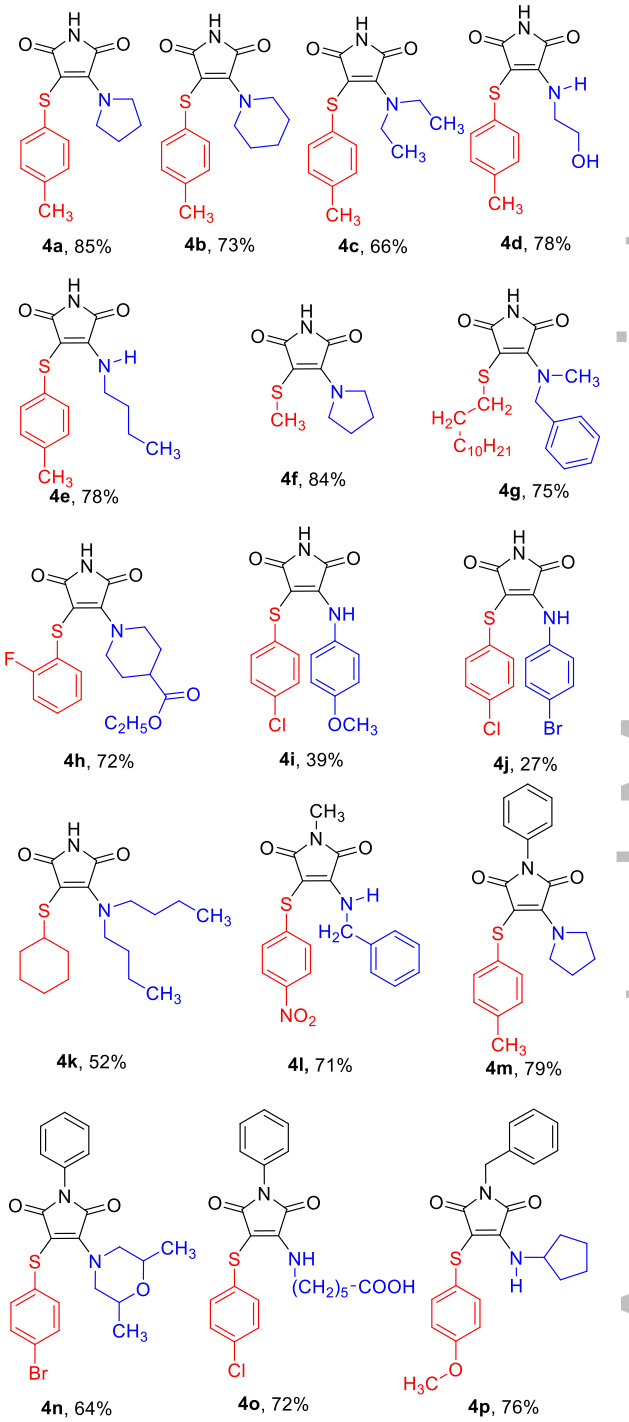
[a] Reaction conditions: **1a** (2.1 mmol), **2a** (2.0 mmol), **3a** (2.1 mmol), catalyst, solvent (6 mL), O_2 balloon, 6 h.
[b] Isolated yield.
[c] Air condition.

In recent years, there have been significant improvements in the direct thioamination of alkene,[6] alkyne,[7] and aryne[8] for C–N and C–S bond formation. Mizar et al. recently developed efficient thioamination of alkenes mediated by iodine(III) reagents.[6a] Subsequently, highly regio- and stereo-selective intermolecular seleno- and thioamination of alkynes was reported by Zheng.[7a] Yoshida also described a direct thioamination of arynes via reaction with sulfilimines and migratory N-arylation to give o-sulfanylanilines in high yield.[8a] However, to the best of our knowledge, an intermolecular thioamination of maleimides has not yet been reported. The most likely reason is that the maleimides are unstable in the presence of strong acid and alkali, and are apt to polymerize and decompose. [9] Nevertheless, in consideration of our previous studies on maleimides[10] and the importance of the introduction of nitrogen and sulfur functional groups, we report the first direct copper-catalyzed intermolecular thioamination of maleimides with thiols and amines without affecting the olefin bond (Scheme 1c).

Initially, the reaction of *p*-thiocresol **1a**, maleimide **2a** and pyrrolidine **3a** was chosen as a model system to identify and optimize reaction parameters (Table 1). The desired product **4a** was obtained in 37% yield in the presence of CuCl (1 equiv.) in DMSO at 120 ℃ under air for 6 h (entry 1, Table 1). The yield of **4a** dramatically increased to 52% when the reaction was conducted under an oxygen atmosphere (entry 2, Table 1). Clearly, O_2 was beneficial to the efficient formation of **4a**. We next altered several parameters

Table 2. Cu-catalyzed C-H thioamination of maleimides with thiols and amines.[a,b]



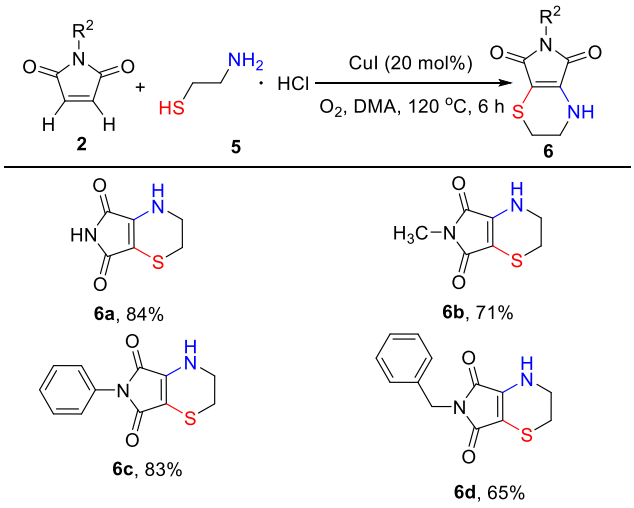


[a] Reaction conditions: **1** (2.1 mmol), **2** (2.0 mmol), **3** (2.1 mmol), CuI (20 mol %), DMA (6 mL), O_2 balloon, 6 h.
[b] Isolated yield.

in an attempt to improve the yield of desired product. First, several catalysts were screened. I_2 and copper salts provided 27-73% isolated yields (entries 2-7, Table 1). CuI was slightly superior to the others and proved to be the best catalyst. The solvent also played a crucial role. Among the solvents tested (DMSO, DMA, MCB, DMF and Dioxane), DMA was the best for this transformation (entries 4, 8-11, Table 1). Subsequent experiments titrating the amount of CuI showed that 20 mol% CuI loading was appropriate (entries 12-14 Table 1). Finally, examination of the effect of the reaction temperature indicated that 120 ℃ was best for the formation of product in the reaction (entries 13, 15-16, Table 1). In addition, none of the desired product **4a** could be obtained in the absence of catalyst (entry 17, Table 1).

With the optimized reaction conditions identified, we next turned our attention to explore the scope of the reaction (Table 2). The reaction is quite general. A variety of substituted aryl or alkyl amines and thiols could be employed for the thioamination of various maleimides. We found that the difference of nucleophilicity of amines played an important role in reaction yield. That is, aliphatic amines had a good yield (**4a-h**, **k-p**, 52-85%), and aromatic amines gave a poor yield (**4i-j**, 27-39%). Although aliphatic amines exhibited high reactivity, unfortunately, the yield of compound (**4k** and **4n**, 52% and 64%) was low due to steric hindrance. Thiophenols with electron-deficient nitro (**4l**) and electron-donating methoxy (**4p**) substituents generally delivered the desired products in comparable yields (71% and 76%, respectively). Moreover, various halogen functional groups (**4h-j**, **4n-o**) were also tolerable, providing useful synthetic handles for further functionalization to complex molecules. Notably, the substituent (e.g., methyl, phenyl, and benzyl) from (NH) maleimides showed no obvious impact on reaction yields (**4l-4p**, 64-79%). We also tested functional group tolerance in the reaction. We found that the hydroxyl, ester,

Table 3. Cu-catalyzed C-H thioamination of maleimides with 2-aminoethanethiol hydrochloride.[a,b]



[a] Reaction conditions: **2** (2.0 mmol), **5** (2.1 mmol), CuI (20 mol %), DMA (6 mL), O_2 balloon, 6 h.
[b] Isolated yield.

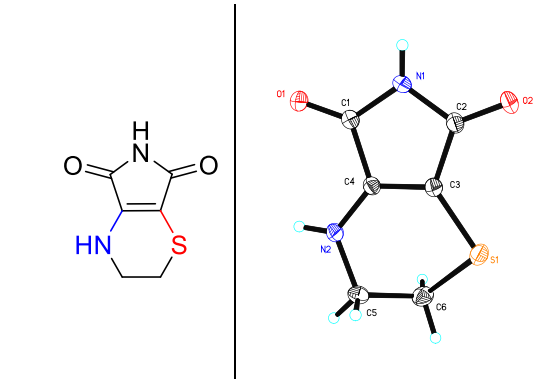
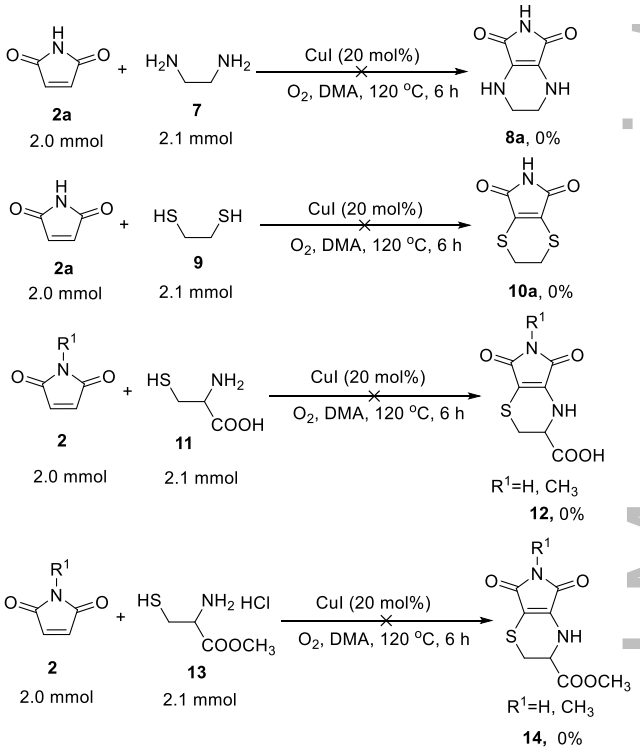


Figure 1. ORTEP view of the X-ray structure of **6a**.



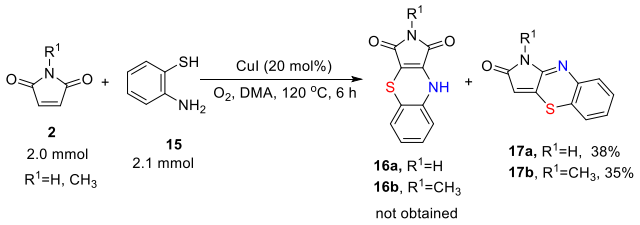
Scheme 2. The reaction of maleimide **2** with 1,2-diaminoethane, 1,2-ethanedithiol, L-cysteine and L-cysteine methyl ester hydrochloride.

ether, and carboxyl groups had no marked effect on the reaction yields (**4d**, **4h**, **4n**, and **4o**, 64%-78%).

Since the pyrrolo[3,4-*b*][1,4]thiazine-5,7(2*H*,6*H*)-diones serve as functional dyes and also show broad spectrum antibacterial and antifungal activities,[11] we next explored the scope of this reaction of maleimides with 2-aminoethanethiol hydrochloride under our optimal conditions (Table 3). The results indicated that maleimides reacted smoothly with 2-aminoethanethiol hydrochloride and provided the desired product in good yields (**6a-6d**, 65%-84%). The compound **6a** was crystallized, and X-ray analysis unambiguously confirmed the structure of thioamination of maleimides (Figure 1).[12] However, the compound **2a** didn't react with 1,2-diaminoethane and 1,2-ethanedithiol to yield the corresponding product **8a** and **10a** in the protocol (Scheme 2). The results rule out the possibility of twice Michael addition and oxidative dehydrogenation processes. In addition, we also tried to use L-cysteine and L-

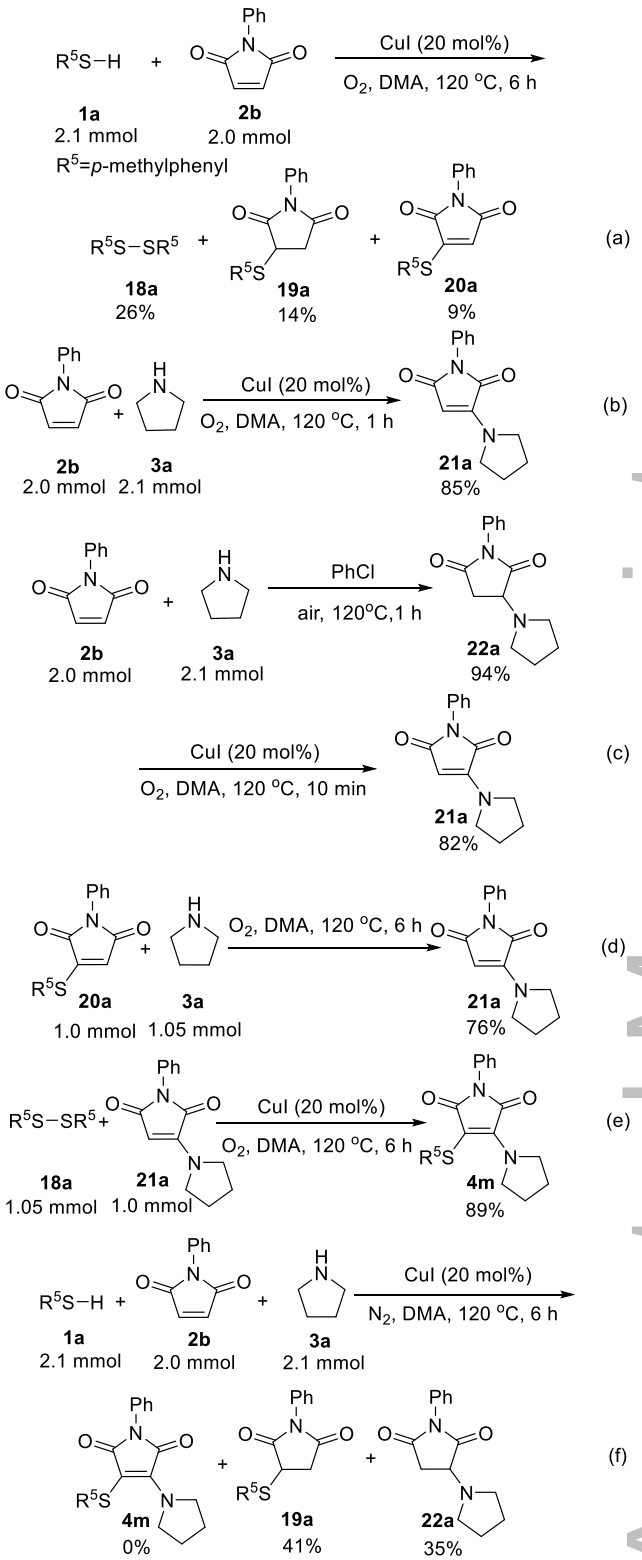
cysteine methyl ester hydrochloride as reaction materials to explore the scope of the reaction. Unfortunately, all of the reactions failed. The reaction results suggested that maleimides could not react with L-cysteine or L-cysteine methyl ester hydrochloride to get the desired products **12** and **14**. The reaction systems always became to black mixtures under our standard reaction condition. The most likely reason is that the L-cysteine and L-cysteine methyl ester hydrochloride have strong coordination ability to cupric ion. They are also easy to be oxidized.

Next, we paid more attention to investigate the reaction of maleimides with 2-aminothiophenol (Scheme 3). The reaction results showed that maleimide could react with 2-aminothiophenol to provide a yellow-white solid. We hope the compound **16a** can be obtained. However, the structure of this compound was assigned to products **17a** by the spectral analysis HRMS, ^{1}H and ^{13}C NMR. The analysis of NMR spectral data suggested six hydrogen and ten carbon signals. Compound **16a** and **17b** have the same amount of hydrogen and carbon. Luckily, MS spectrum gave us a clue to determine the structure of product. Furthermore, EI spectrum of this compound showed a molecular ion at 202 (M^+). High-resolution mass spectrum suggested a molecular formula of $C_{10}H_6N_2OS$. The molecular formula is consistent with compound **17a**. In order to understand this problem, we used N-methylmaleimide to run this reaction. Compound **17b** was obtained with 35% yield on the base of spectrum analysis. We believe the products **17** were synthesized under our standard condition (see supporting information for details).



Scheme 3. The reaction of maleimide **2** with 2-aminothiophenol **15**

To acquire insight into the reaction mechanism, control experiments were conducted. First, a large amount of bis(4-methylphenyl)disulphide **18a** was obtained in the reaction between *p*-thiocresol **1a** and N-phenylmaleimide **2b** under standard conditions in addition to the thia-Michael addition product (**19a**, 14%) and its oxidative dehydrogenation product (**20a**, 9%) (Scheme 4a). Second, N-phenylmaleimide **2b** reacted with pyrrolidine **3a** to produce 1-phenyl-3-(pyrrolidin-1-yl)-1*H*-pyrrole-2,5-dione (**21a**, 85%) in one hour (Scheme 4b). We found that the aza-Michael addition product **22a** could be oxidized to **21a** with good yield quickly under optimal conditions (Scheme 4c). At the same time, the product **20a** could further react with **3a** to produce **21a** in 76% yield by



Scheme 4. Control experiments.

nucleophilic substitution (Scheme 4d).[13] The subsequent employment of **21a** with bis(4-methylphenyl)disulfide **18a** proved that product **4m** could be obtained with good yield (Scheme 4e). However, none of target product **4m** was detected under an N_2 atmosphere (Scheme 4f). These results show that (i) the compounds **18a**, **19a**, **20a**, **21a** and **22a** are the intermediates in the reaction, (ii) and that

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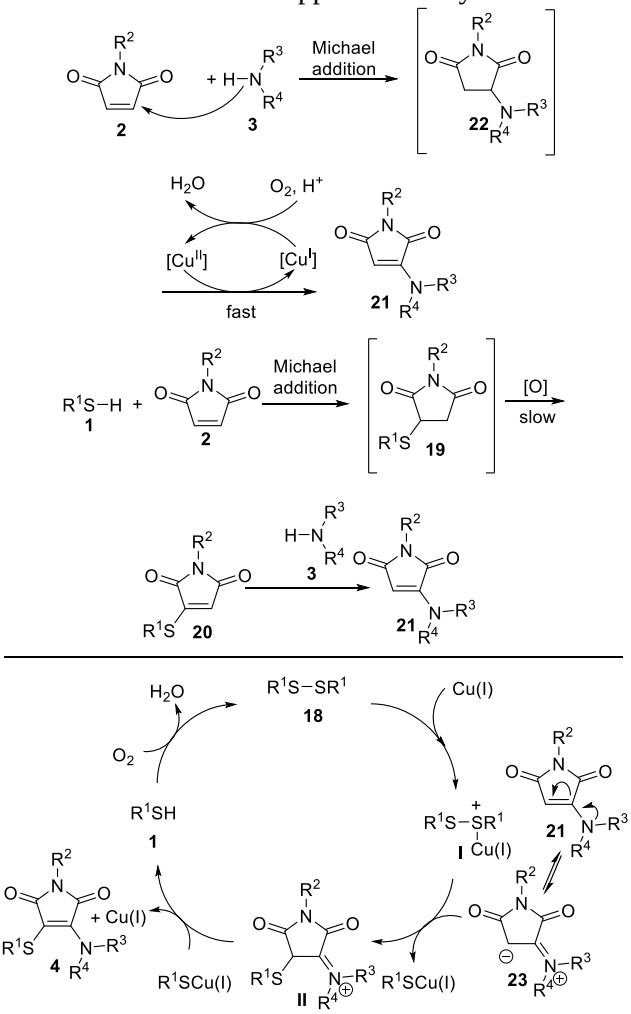
oxygen plays an important role in the formation of product (see supporting information for details).

Based on the above evidence and reported mechanistic studies on copper chemistry with thiols



Scheme 5. Proposed reaction mechanism.

and amines, a plausible pathway was proposed as shown in Scheme 5. On one hand, the amines **3** underwent aza-Michael addition with maleimides **2** to form 3-aminosuccinimides **22**, which produced 3-aminomaleimides **21** by copper catalyzed aerobic oxidative dehydrogenation.[14] Because the reaction was conducted under O_2, the Cu(I) species in this reaction was easily oxidized to Cu(II), showing that the reaction can be catalyzed by copper catalyst with O_2 as the terminal oxidant.[15] Alternatively, compound **21** also could be obtained via the nucleophilic substitution between amines **3** and 3-thiomaleimides, which have been synthesized by thia-Michael addition and oxidative dehydrogenation processes. However, the oxidative dehydrogenation process of Michael adduct **19** is harder under these conditions according to our previous studies.[10b] Next, the copper(I) catalyst interacts with disulphide **18** to generate intermediate **I**.[16] The region-selective electrophilic attack of **I** on 3-aminomaleimides **21** at the 4-position via its isomeric version **23** results in the formation of the intermediate **II**, which deprotonates to give the corresponding target products **4** and the copper catalyst is regenerated.[17] At the same time, the oxidation of the in situ generated R^1SH by O_2 reproduces disulphide **18**.[18] Oxygen plays an important role in the regeneration of the catalytically active species as well as the oxidative dimerization of the thiols.

In summary, we have developed an efficient strategy for direct C(sp^2)−H difunctionalization of maleimides with thiols and amines. This methodology is very general, practical, environmentally friendly and features high atom economy as well as excellent functional group tolerance. Further biological activity evaluation of these compounds and application of this methodology for the preparation of new potent bioactive molecules are ongoing in our group.

Experimental Section

General Information

All experiments were carried out under O_2 atmosphere. All chemicals and solvents used in our experiments were obtained from commercial suppliers and used without further purification. Melting points were determined with RY-1 apparatus and uncorrected. IR spectra were recorded as KBr pellets on a Shimadzu model 470 spectrophotometer. NMR (^1H and ^{13}C) spectra were recorded using a Bruker AV 400 or 600 MHz spectrometer in DMSO-d_6 or $CDCl_3$ with TMS as internal standard. Chemical shifts (δ) were recorded in ppm. Mass spectra were acquired on Waters micromass GCT premier, Agilent technologies 5973N and thermo Fisher scientific LTQ FT Ultra.

Typical Procedure for the Synthesis of 3-Amino-4-thiomaleimides 4

A solution of CuI (0.4 mmol), thiols **1** (2.1 mmol), maleimides **2** (2.0 mmol) and amines **3** (2.1 mmol) in 6 mL of DMA was stirred at 120 ºC for 6 h under O_2. After cooling down to room temperature, 10 mL of water were added, and the resulting mixture was extracted with ethyl acetate (3 × 10 mL). The organic phases were dried with anhydrous Na_2SO_4, concentrated and purified by silica gel column chromatography (eluent: ethyl acetate-PE, 1: 10~35) to yield the pure product **4**.

Typical Procedure for the Synthesis of 3,4-Dihydropyrrolo[3,4-*b*][1,4]thiazine-5,7(2*H*,6*H*)-diones 6

A solution of CuI (0.4 mmol), maleimides **2** (2.0 mmol) and 2-aminoethanethiol hydrochloride **5** (2.1 mmol) in 6 mL of DMA was stirred at 120 ºC for 6 h under O_2. After cooling down to room temperature, 10 mL of water were added, and the resulting mixture was extracted with ethyl acetate (3 × 10 mL). The organic phases were dried with anhydrous Na_2SO_4, concentrated and purified by silica gel

column chromatography (eluent: ethyl acetate-PE, 1: 5~15) to yield the pure product **6**.

Acknowledgements

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[12] CCDC 1549531 (**6a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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UPDATE

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Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Zhen-Hua Yang, Hong-Ru Tan, Yu-Long An, Yu-Wei Zhao, Hao-Peng Lin, and Sheng-Yin Zhao*