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Copper-catalyzed direct thiolation of xanthines and related heterocycles with disulfides

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ABSTRACT

A novel copper-catalyzed, base-free direct thiolation of xanthines and related heterocycles is described, featuring the use of inexpensive $Cu(OAc)_2{\cdot}H_2O$ as the catalyst, O_2 as a clean and cheap oxidant, and easy-to-handle disulfides as the thiolation reagents. It works well for both aryl and alkyl disulfides. Moreover, the resultant products can be converted into 8-(hetero)aryl- or alkenyl-substituted xanthines in good yields via the Liebeskind–Srogl coupling reaction.

Xanthines, including caffeine, theophylline, and theobromine, are important heterocycles commonly found in a wide range of agrochemically useful and pharmaceutically active compounds. Among these, the C-8 substituted xanthines as high affinity and selective adenosine receptor antagonists[1] have gained much attention. Undoubtedly, the direct C–H bond activation is the most straightforward and efficient approach to these motifs. Thus, over the past few years, a number of Pd or Cu-promoted direct C-8 arylation of xanthines have been achieved with aryl (pseudo)halides,[2] arylboronic acids,[3] arylsilanes,[4] arylsulfonyl derivatives,[5] or (hetero)arenes.[6] In contrast, there are only limited examples on the synthesis of heteroatom-substituted xanthines so far.[7]

Petzer reported that C-8 substitution of xanthines with a thioether group might exhibit an enhanced MAO-B inhibition activity.[8] However, as far as the thiolation of xanthines is concerned, it usually involves the transformation of prefunctionalized xanthines with thiols or thiolates, which suffers from low step and atom economy.[9] Moreover, thiols often possess an odd smell and are susceptible to undergo the oxidative homocoupling reaction. Recently, the direct thiolation of C–H bonds,[7b,10] including the non-chelation-assisted ones,[7b,10b,i,j] has become an intriguing and effective alternative to access sulfides. In this regard, Bolm[7b] reported an elegant metal-free direct thiolation of xanthines and related heterocycles very recently; however, the use of excess strong base, moderate yield (55% for caffeine), and incompatibility with alkyl disulfides limit the synthetic utility of this method. To overcome these drawbacks, we report here a copper-catalyzed, base-free C-8 direct thiolation of xanthines and related heteroarenes featuring the use of inexpensive $Cu(OAc)_2{\cdot}H_2O$ as the catalyst and O_2 as a clean and cheap oxidant. Notably, both aryl and alkyl disulfides can be employed as effective thiolation reagents.

Initially, the reaction of caffeine (**1a**) with diphenyldisulfide (**2a**) was chosen as the model system to evaluate the reaction parameters. As shown in Table 1, the copper sources had a significant influence on the reaction, and $Cu(OAc)_2{\cdot}H_2O$ appeared to be the best choice, delivering **3aa** in 70% yield (Table 1, entries 1–5). A brief survey of the solvents, including polar and nonpolar solvents, revealed that a better yield (78%) could be obtained in xylene (Table 1, entries 6–10). Furthermore, the yield increased to 85% when the reaction was performed under an O_2 atmosphere, while under N_2, only 30% of **3aa** was isolated (Table 1, entry 10).

To reduce the catalyst loading, a variety of additives were investigated, and we were pleased to find that **3aa** was obtained in 95% yield when 2 mol % of AgOAc was added (Table 1, entry 16). On the other hand, Lewis acids,[11] such as $FeCl_3$ and $AlCl_3{\cdot}6H_2O$, were totally ineffective (Table 1, entries 17 and 18). It should be noted that the reaction did not occur in the absence of $Cu(OAc)_2{\cdot}H_2O$. Finally, the optimized reaction conditions consisted of 20 mol % of $Cu(OAc)_2{\cdot}H_2O$, 2 mol % of AgOAc, and xylene under O_2 at 145 °C for 15 h.[12]

With the optimum reaction conditions in hand, the scope of this reaction with respect to xanthines was investigated (Table 2). In general, various *N*-substituted xanthines underwent the thiolation reaction smoothly and generated the thiolated xanthines in good to excellent yields. As an example, thiolation of benzylic theophylline led to **3ba** in 95% yield (Table 2, **3ba**).

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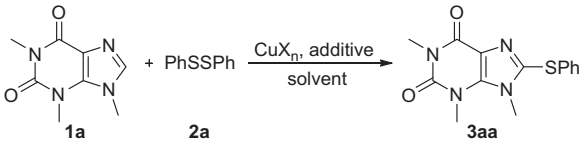
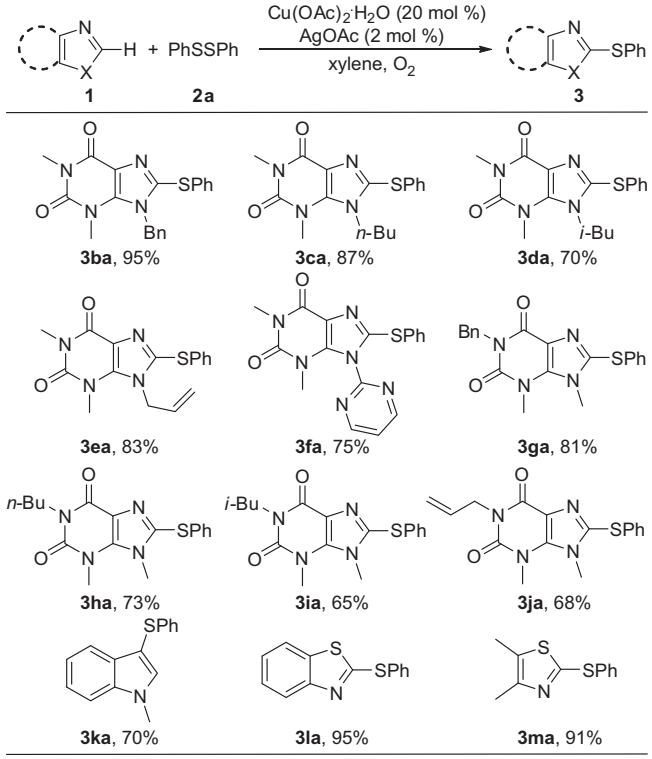
Table 1
Screening of the reaction conditions[a]



Entry	CuX_n (mol %)	Additive (mol %)	Solvent	Yield[b] (%)
1	CuI (100)	/	NMP	<5
2	$CuBr_2$ (100)	/	NMP	18
3	$CuCl_2$ (100)	/	NMP	25
4	$CuSO_4$ (100)	/	NMP	37
5	$Cu(OAc)\cdot H_2O$ (100)	/	NMP	70
6	$Cu(OAc)_2\cdot H_2O$ (100)	/	DMSO	72
7	$Cu(OAc)_2\cdot H_2O$ (100)	/	DMF	60
8	$Cu(OAc)_2\cdot H_2O$ (100)	/	DMAc	75
9	$Cu(OAc)_2\cdot H_2O$ (100)	/	Toluene	74
10	$Cu(OAc)_2\cdot H_2O$ (100)	/	Xylene	78 (85)[c] (30)[d]
11	$Cu(OAc)_2\cdot H_2O$ (20)	/	Xylene	40[c]
12	$Cu(OAc)_2\cdot H_2O$ (20)	DDQ (100)	Xylene	<5[c]
13	$Cu(OAc)_2\cdot H_2O$ (20)	$K_2S_2O_8$ (100)	Xylene	23[c]
14	$Cu(OAc)_2\cdot H_2O$ (20)	Ag_2CO_3 (100)	Xylene	42[c]
15	$Cu(OAc)_2\cdot H_2O$ (20)	AgOAc (100)	Xylene	72[c]
16	$Cu(OAc)_2\cdot H_2O$ (20)	AgOAc (2)	Xylene	95[c]
17	$Cu(OAc)_2\cdot H_2O$ (20)	$AlCl_3\cdot 6H_2O$ (2)	Xylene	<5[c]
18	$Cu(OAc)_2\cdot H_2O$ (20)	$FeCl_3$ (2)	Xylene	<5[c]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.3 mmol), CuX_n (20–100 mol %) and additive (0–100 mol %) in 2 mL of solvent at 145 °C for 15 h.
[b] Isolated yield.
[c] Under O_2.
[d] Under N_2.

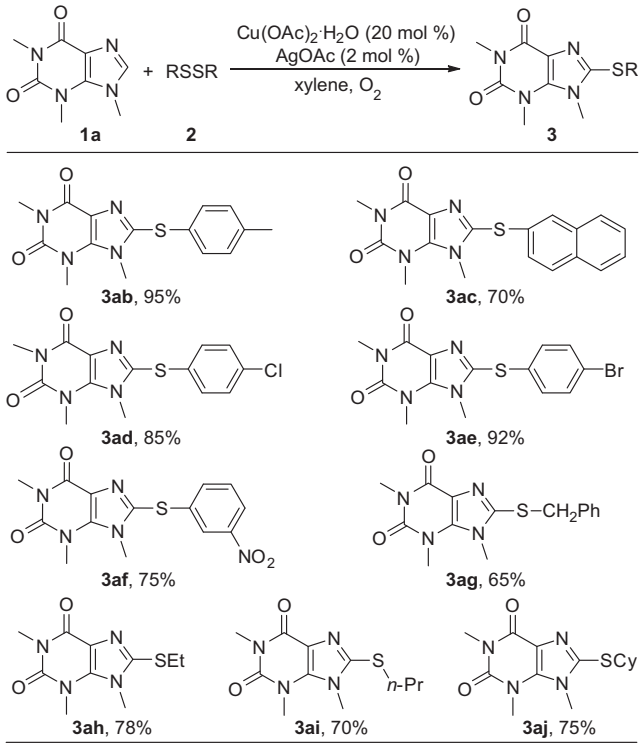
Table 2
Cu-catalyzed thiolation of xanthines and related heterocycles with **2a**[a]



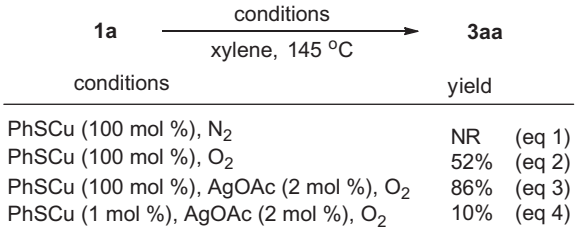
[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.3 mmol), $Cu(OAc)_2\cdot H_2O$ (20 mol %) and AgOAc (2 mol %) in 2 mL of xylene at 145 °C for 15 h.

The steric hindrance had some effect on the reaction. For example, *N*-*n*-Bu-substituted xanthine **1c** and *N*-*i*-Bu-substituted xanthine **1d** produced **3ca** and **3da** in respective yields of 87% and 70% (Table 2, **3ca** and **3da**). Interestingly, the coupling of *N*-methyl indole (**1k**) with **2a** gave rise to the C-3 thiolated product **3ka**[13] in 70% yield (Table 2, **3ka**). Under the standard conditions, the reaction of benzothiazole (**1l**) and 4,5-dimethylthiazole (**1m**) furnished the desired products in excellent yields (Table 2, **3la** and **3ma**).

Table 3
The scope of disulfides **2**[a]



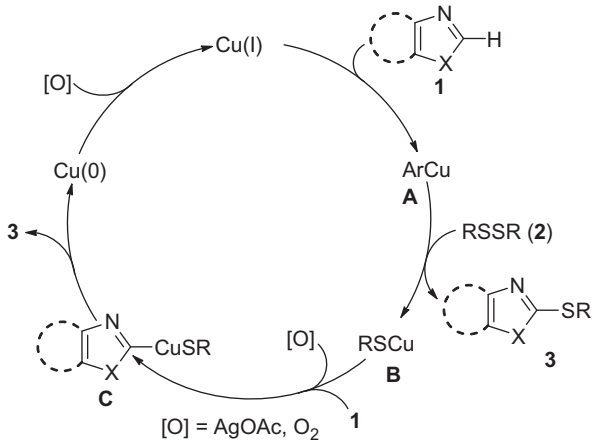
[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.3 mmol), $Cu(OAc)_2\cdot H_2O$ (20 mol %) and AgOAc (2 mol %) in 2 mL of xylene at 145 °C for 15 h.



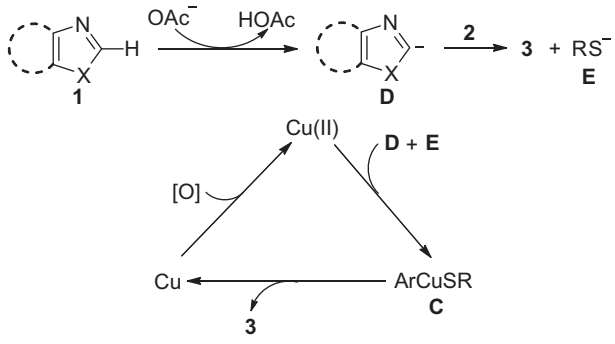
Scheme 1. Preliminary mechanism study.

Then, the disulfide component was varied and the results were summarized in Table 3. To our delight, all aromatic disulfides were found to undergo the thiolation reaction with **1a** smoothly. Both 4-chlorophenyl disulfide (**2d**) and 4-bromophenyl disulfide (**2e**) gave high yields of thiolated products without affecting the C–Hal bonds (Table 3, **3ad** and **3ae**), which could be used for installing other functional groups via the transformations of the C–Hal bonds. An electron-withdrawing group such as NO_2 was also well-tolerated, giving rise to **3af** in 75% yield (Table 3, **3af**). Moreover, the aliphatic disulfides were effective coupling partners for this transformation, and even for the steric demanding substrate **2j**, a good yield was still observed (Table 3, **3aj**). Notably, the two RS groups in disulfides **2** could be utilized for the thiolation reaction, thus providing an atom-economical entry to the synthesis of sulfides.

To gain insights into the mechanism of this reaction, we conducted the following experiments. Treating **1a** with 100 mol % of



Scheme 2. A possible mechanism.



Scheme 3. An alternative mechanism.

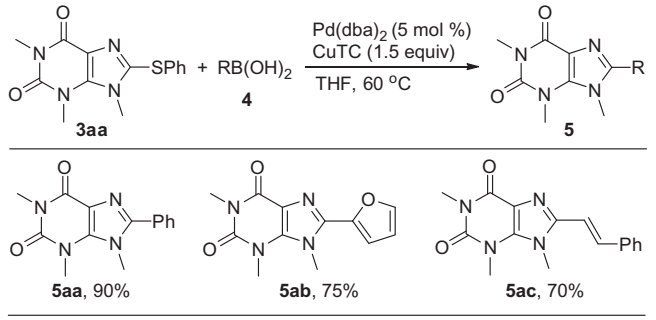
PhSCu[10b,i] under O_2 atmosphere provided 52% of **3aa**, while the reaction did not occur by replacing O_2 with N_2 (Scheme 1, Eqs. 1 and 2). The yield further increased to 86% when 2 mol % of AgOAc was added (Scheme 1, Eq. 3). Moreover, the reaction performed with 1 mol % of PhSCu and 2 mol % of AgOAc under O_2 resulted in **3aa** in 10% yield (Scheme 1, Eq. 4).

Based on the above results and previous reports,[10b,i] a plausible mechanism for this Cu-catalyzed thiolation reaction is illustrated in Scheme 2. Initially, the cupration of **1** forms an intermediate **A**, which reacts with disulfides **2** to generate the thiolation products **3** and concurrent formation of RSCu (**B**). Subsequently, the oxidation of **B** followed by cupration of **1** produces the species **C**. Finally, the reductive elimination of **C** affords **3** and Cu(0) which can be oxidized to Cu(I) by O_2 with the help of AgOAc (Scheme 2).

Meanwhile, in view of a recent work from Bolm,[7b] an alternative mechanism initiated by the deprotonation of xanthines can be proposed in Scheme 3, which consists of the following steps: (1) deprotonation of xanthines **1** forming an anion intermediate **D**; (2) nucleophilic substitution of **2** with **D** generating **3** as well as RS^- (**E**); (3) reaction of Cu(II) with **D** and **E** providing the species **C**; (4) reductive elimination of **C** leading to the thiolation products **3** and Cu(0); and (4) regeneration of the Cu(II) catalyst via oxidation of Cu(0) with AgOAc and O_2 (Scheme 3). So far, the detailed mechanism is still not clear.

Having established a facile route to sulfanylxanthines, the applicability of this protocol was studied (Table 4). In view of the fact that 8-(hetero)aryl-substituted caffeines are highly potent and selective antagonists at human A_2B adenosine receptors,[1] the Liebeskind–Srogl coupling reactions[14] of **3aa** with $PhB(OH)_2$ and 2-furylboronic acid were carried out, producing **5aa** and **5ab** in

Table 4
Transformations of sulfanylxanthines[a]



[a] Reaction conditions: **3** (0.2 mmol), **4** (0.3 mmol), $Pd(dba)_2$ (0.01 mmol), CuTC (1.5 equiv), THF, 60 °C, 24 h.

90% and 75% yields, respectively (Table 4, **5aa** and **5ab**).[15] Moreover, 8-styrylxanthines, a type of A_{2A} AR antagonists,[1a,16] could also be synthesized via this protocol. For instance, (*E*)-styrylboronic acid reacted with **3aa** successfully to give (*E*)-8-styryl-l,3,7-trimethylxanthine (**5ac**) in 70% yield (Table 4, **5ac**).

In conclusion, we have developed a copper-catalyzed, base-free direct thiolation of xanthines and related heterocycles featuring the use of inexpensive $Cu(OAc)_2{\cdot}H_2O$ as the catalyst, O_2 as a clean and cheap oxidant, and air stable as well as easy-to-handle disulfides as the thiolation reagents. Both aryl and alkyl disulfides are suitable substrates for this thiolation reaction. Furthermore, this protocol provides a facile and effective alternative to construct 8-(hetero)aryl- or alkenyl-substituted xanthines using the Liebeskind–Srogl coupling reaction. Further investigations on the reaction mechanism are currently undergoing in our group.

Acknowledgments

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Supplementary data

Supplementary data (experimental details, NMR spectra, and analytical data of products **3** and **5**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.08.097.

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12. *Representative procedure for the Cu-catalyzed direct thiolation of xanthines and related heterocycles:* To a reaction tube charged with xanthines (0.5 mmol), disulfides (0.3 mmol), $Cu(OAc)_2{\cdot}H_2O$ (20 mg, 20 mol %), and AgOAc (1.7 mg, 2 mol %) was added 2 mL of xylene. After stirring at 145 °C for 15 h under an O_2 atmosphere, the reaction mixture was concentrated and purified by flash column chromatography on silica gel (dichloromethane/acetone = 20:1) to give 143.5 mg (yield: 95%) of compound **3aa** as a white solid, mp: 147–149 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.29–7.37 (m, 5H), 3.93 (s, 3H), 3.57 (s, 3H), 3.40 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 155.0, 151.4, 148.1, 146.4, 130.9, 130.5, 129.6, 128.3, 109.6, 33.2, 29.9, 28.0.
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15. *Representative procedure for the Liebeskind–Srogl coupling of **3aa** with boronic acids:* To a mixture of **3aa** (0.2 mmol), boronic acid (0.15 equiv, 0.3 mmol), Cu (I) thiophene-2-carboxylate (CuTC) (57.2 mg, 0.3 mmol) and $Pd(dba)_2$ (5.8 mg, 0.01 mmol) was added 2 mL of dry THF. After stirring at 60 °C for 24 h under nitrogen atmosphere, the reaction mixture was concentrated and purified by flash column chromatography on silica gel (dichloromethane/acetone = 20:1) to give 48.6 mg (yield: 90%) of compound **5aa** as a white solid, mp: 180–181 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.70–7.68 (m, 2H), 7.54-7.53 (m, 3H), 4.07 (s, 3H), 3.65 (s, 3H), 3.45 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 155.4, 152.0, 151.5, 148.0, 130.3, 129.1, 128.8, 128.1, 108.4, 33.8, 29.7, 27.9.
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