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Tetrahedron Letters

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## Copper-catalyzed direct thiolation of xanthenes and related heterocycles with disulfides

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## ARTICLE INFO

## Article history:

Received 4 June 2013

Revised 20 August 2013

Accepted 25 August 2013

Available online xxx

## Keywords:

Xanthenes

Thiolation

Copper

Disulfides

## ABSTRACT

A novel copper-catalyzed, base-free direct thiolation of xanthenes and related heterocycles is described, featuring the use of inexpensive  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  as the catalyst,  $\text{O}_2$  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 xanthenes in good yields via the Liebeskind–Srogl coupling reaction.

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Xanthenes, 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 xanthenes as high affinity and selective adenosine receptor antagonists<sup>1</sup> 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 xanthenes have been achieved with aryl (pseudo)halides,<sup>2</sup> arylboronic acids,<sup>3</sup> arylsilanes,<sup>4</sup> arylsulfonyl derivatives,<sup>5</sup> or (hetero)arenes.<sup>6</sup> In contrast, there are only limited examples on the synthesis of heteroatom-substituted xanthenes so far.<sup>7</sup>

Petzer reported that C-8 substitution of xanthenes with a thioether group might exhibit an enhanced MAO-B inhibition activity.<sup>8</sup> However, as far as the thiolation of xanthenes is concerned, it usually involves the transformation of prefunctionalized xanthenes with thiols or thiolates, which suffers from low step and atom economy.<sup>9</sup> Moreover, thiols often possess an odd smell and are susceptible to undergo the oxidative homocoupling reaction. Recently, the direct thiolation of C–H bonds,<sup>7b,10</sup> including the non-chelation-assisted ones,<sup>7b,10b,ij</sup> has become an intriguing and effective alternative to access sulfides. In this regard, Bolm<sup>7b</sup> reported an elegant metal-free direct thiolation of xanthenes 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 xanthenes and related heteroarenes featuring the use of inexpensive  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  as the catalyst and  $\text{O}_2$  as a clean and cheap oxidant. Notably, both aryl and alkyl disulfides can be employed as effective thiolation reagents.

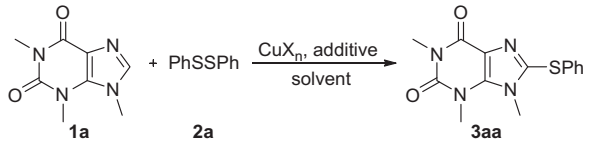
Initially, the reaction of caffeine (**1a**) with diphenyldisulfide (**2a**) was chosen as the model system to evaluate the reaction parameters. As shown in Table 1, the copper sources had a significant influence on the reaction, and  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  appeared to be 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  $\text{O}_2$  atmosphere, while under  $\text{N}_2$ , 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,<sup>11</sup> such as  $\text{FeCl}_3$  and  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ , were totally ineffective (Table 1, entries 17 and 18). It should be noted that the reaction did not occur in the absence of  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ . Finally, the optimized reaction conditions consisted of 20 mol % of  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ , 2 mol % of AgOAc, and xylene under  $\text{O}_2$  at 145 °C for 15 h.<sup>12</sup>

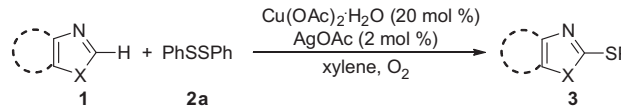
With the optimum reaction conditions in hand, the scope of this reaction with respect to xanthenes was investigated (Table 2). In general, various *N*-substituted xanthenes underwent the thiolation reaction smoothly and generated the thiolated xanthenes in good to excellent yields. As an example, thiolation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

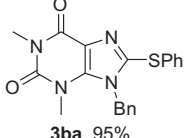
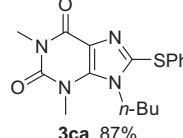
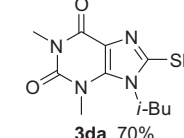
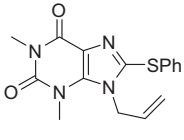
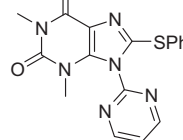
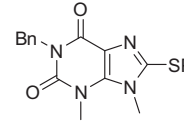
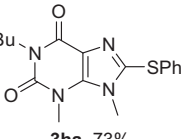
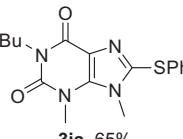
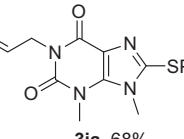
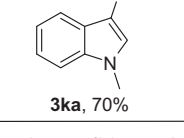
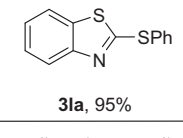
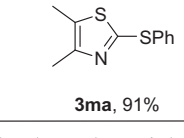
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**Table 1**  
Screening of the reaction conditions<sup>a</sup>


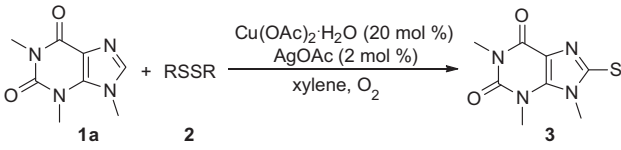
Entry	CuX <sub>n</sub> (mol %)	Additive (mol %)	Solvent	Yield <sup>b</sup> (%)
1	CuI (100)	/	NMP	<5
2	CuBr <sub>2</sub> (100)	/	NMP	18
3	CuCl <sub>2</sub> (100)	/	NMP	25
4	CuSO <sub>4</sub> (100)	/	NMP	37
5	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O (100)	/	NMP	70
6	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O (100)	/	DMSO	72
7	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O (100)	/	DMF	60
8	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O (100)	/	DMAc	75
9	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O (100)	/	Toluene	74
10	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O (100)	/	Xylene	78 (85) <sup>c</sup> (30) <sup>d</sup>
11	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O (20)	/	Xylene	40 <sup>c</sup>
12	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O (20)	DDQ (100)	Xylene	<5 <sup>c</sup>
13	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O (20)	K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> (100)	Xylene	23 <sup>c</sup>
14	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O (20)	Ag <sub>2</sub> CO <sub>3</sub> (100)	Xylene	42 <sup>c</sup>
15	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O (20)	AgOAc (100)	Xylene	72 <sup>c</sup>
16	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O (20)	AgOAc (2)	Xylene	95 <sup>c</sup>
17	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O (20)	AlCl <sub>3</sub> ·6H <sub>2</sub> O (2)	Xylene	<5 <sup>c</sup>
18	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O (20)	FeCl <sub>3</sub> (2)	Xylene	<5 <sup>c</sup>

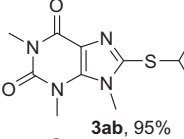
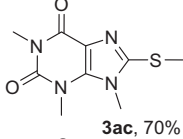
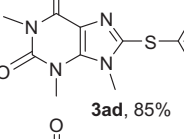
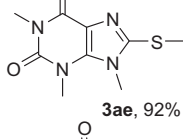
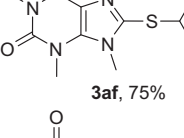
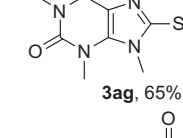
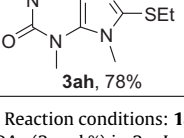
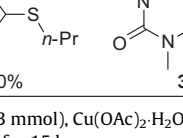
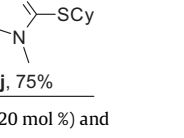
<sup>a</sup> Reaction conditions: **1a** (0.5 mmol), **2a** (0.3 mmol), CuX<sub>n</sub> (20–100 mol %) and additive (0–100 mol %) in 2 mL of solvent at 145 °C for 15 h.<sup>b</sup> Isolated yield.<sup>c</sup> Under O<sub>2</sub>.<sup>d</sup> Under N<sub>2</sub>.**Table 2**  
Cu-catalyzed thiolation of xanthenes and related heterocycles with **2a**<sup>a</sup>


		
<b>3ba</b> , 95%	<b>3ca</b> , 87%	<b>3da</b> , 70%
		
<b>3ea</b> , 83%	<b>3fa</b> , 75%	<b>3ga</b> , 81%
		
<b>3ha</b> , 73%	<b>3ia</b> , 65%	<b>3ja</b> , 68%
		
<b>3ka</b> , 70%	<b>3la</b> , 95%	<b>3ma</b> , 91%

<sup>a</sup> Reaction conditions: **1** (0.5 mmol), **2a** (0.3 mmol), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (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%

**Table 3**  
The scope of disulfides **2**<sup>a</sup>


		
<b>3ab</b> , 95%	<b>3ac</b> , 70%	
		
<b>3ad</b> , 85%	<b>3ae</b> , 92%	
		
<b>3af</b> , 75%	<b>3ag</b> , 65%	
		
<b>3ah</b> , 78%	<b>3ai</b> , 70%	<b>3aj</b> , 75%

<sup>a</sup> Reaction conditions: **1a** (0.5 mmol), **2** (0.3 mmol), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (20 mol %) and AgOAc (2 mol %) in 2 mL of xylene at 145 °C for 15 h.

1a	conditions	3aa
	xylene, 145 °C	
conditions		yield
PhSCu (100 mol %), N <sub>2</sub>		NR (eq 1)
PhSCu (100 mol %), O <sub>2</sub>		52% (eq 2)
PhSCu (100 mol %), AgOAc (2 mol %), O <sub>2</sub>		86% (eq 3)
PhSCu (1 mol %), AgOAc (2 mol %), O <sub>2</sub>		10% (eq 4)

**Scheme 1.** Preliminary mechanism study.

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**<sup>13</sup> 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**).

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<sub>2</sub> 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

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