## Letter

# Copper-Catalyzed Acetylation of Electron-Rich Phenols and Anilines

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**Abstract** An approach has been developed for the copper-catalyzed acetylation of phenols and anilines with potassium thioacetate as an acetylating reagent. Although only electron-rich phenols and anilines are compatible with this protocol, the reaction can provide moderate to high yields under mild conditions. Compared with other acetylating reagents, the current reagent has certain advantages, such as its low cost, easy availability, stability, insensitivity to water or air, and ease of storage.

**Key words** acetylation, phenols, anilines, copper catalysis, potassium thioacetate, butyl nitrite

The acetylation of phenols and anilines is a fundamental transformation in organic synthesis, as this is a common method for protecting these functional groups protected during multistep syntheses.<sup>1</sup> Aryl acetates and acetamides are also widely used as agrochemicals, medicines, preservatives, plasticizers, or polymer components.<sup>2</sup>

Much effort has been devoted to the study of acetylation reactions, and various acetylating reagents have been explored for this transformation in recent decades. However, there is still a considerable demand for the development of inexpensive, simple, and ecofriendly acylation processes.

Acetic anhydride<sup>3</sup> and acetyl chloride<sup>4</sup> are the most commonly used sources of acetyl groups. Transformations using these reagents are usually performed in the presence of either basic or acidic catalysts. These reactions, although still widely used in industry and academia, suffer from such problems as the use of toxic or corrosive acetylating reagents, the formation of waste acids with poor atom econo-



X = NH, O

Yields : 50–93% 17 examples

my, and sensitivity to water or air. To comply with the principles of green synthesis and atomic economy, inexpensive carboxylic acids<sup>5</sup>, esters,<sup>6</sup> and alcohols<sup>7</sup> have been developed as reagents for acetylation reactions. For examples, Thakur and co-workers reported the synthesis of acetamide with acetic acid catalyzed by nanoparticulate Al<sub>2</sub>O<sub>3</sub> under solvent-free conditions.<sup>5a</sup> Sanz Sharley and Williams showed that acetic acid is an effective catalyst for the acetylation of amines with either ethyl acetate or butyl acetate as the acetyl source.<sup>6b</sup> Zhang and co-workers reported the aerobic oxidative coupling of amines with alcohols catalyzed by resin-supported Au-Pd nano-alloy catalysts, with the alcohols acting as acylating agents.<sup>7</sup> However, the relatively low reactivity of acids or esters and the reversible nature of the reaction equilibrium resulted in only partial conversion. Therefore, the continuous removal of water or alcohols is a critical factor in driving the reaction. To overcome these problems, the use of enol esters as acylating agents has recently been reported; in this reaction, the enol byproduct formed in the reaction was rapidly transformed into the corresponding aldehyde, which rapidly escaped from the equilibrium system.<sup>8</sup> Sharma and co-workers reported a DABCO-catalyzed esterification of phenols with vinyl acetate as an acetylating reagent under microwave conditions.<sup>8b</sup> In addition, 1,3-diketone compounds have been employed in acetylations through cleavage of the C-C single bond, releasing a ketone molecule.<sup>9</sup> Wang and co-workers developed a metal-free method for the acetylation of anilines with 1,3-diketones as acylating reagents promoted by H<sub>2</sub>O<sub>2</sub> as a sole oxidant at room temperature in water.<sup>9a</sup> Following this work, various catalytic systems were explored for the acetylation of anilines with 1,3-diketones.<sup>9c,d</sup> In acJ. Zhang et al.

cord with this strategy of releasing a small molecule, Sumathi and co-workers reported an efficient method for the acetylation of amines with *N*,*N*-dimethylacetamide (DMAc) as a source of an acetyl moiety in the presence of carbonyldiimidazole (CDI); this reaction was accompanied by the release of dimethylamine gas.<sup>10</sup>

Generally, thioacetic acid or potassium thioacetate are used as sources of thioacetate anions, commonly used as nucleophilic partners in substitution reactions<sup>11a-d</sup> or crosscoupling reaction to give organic thioacetates.<sup>11e-g</sup> Recently, these reagents have been used as sources of acetyl groups for the synthesis of amides through metal-catalyzed crosscoupling reaction with amines.<sup>12</sup> Two activated intermediates from thioacetic acid or potassium thioacetate can be present in these reactions: metal complexes of thioacetic acid<sup>12b,c</sup> or diacetyl disulfide.<sup>12d,e</sup> For examples, Gopi and coworkers reported the copper-catalyzed acetylation of amines with thioacetic acid as an acetvlating reagent.<sup>12b,c</sup> Tan and co-workers developed a visible-light-promoted photoredox-catalyzed method for the synthesis of amides with potassium thioacetate.<sup>12d</sup> To the best of our knowledge, the application of these reagents to the acetylation of phenols and alcohols has not yet been reported. Here, we report a simple copper-catalyzed acetylation of phenols and anilines with potassium thioacetate as an acetylating reagent.

We began our investigations by examining the reaction of 2-naphthol (1a) with potassium thioacetate (2a). First, various solvents were screened in the absence of a catalyst (Table1, entries 1-4). To our surprise, the target product 2naphthyl acetate was obtained in 68% yield in MeCN at 80 °C under air (entry 1), whereas only traces of the product were detected in other solvents (entries 2-4). Next, various copper salts were examined as catalysts for the reaction and were shown to improve the yield (entries 5-9) with the highest yield being obtained when  $Cu(OAc)_2 \cdot H_2O$  was used as the catalyst (entry 9). We also found that the amount of **2a** had a marked impact on the reaction (entries 9–11), and when the amount of **2a** was increased to 3.0 equivalents, a 93% yield was obtained (entry 11). Finally, we investigated the effect of the temperature on the reaction (entries 12-15). The optimal reaction temperature was found to be 80 °C, significantly lower yields being obtained at other temperatures, especially room temperature, at which the vield was only 39%.

With the best reaction conditions in hand, we expanded the scope of the method to various naphthols and phenols. We found that this reaction gave moderate to high yields from electron-rich naphthols and phenols (Table 2). A series of functional groups were tolerated including chloro, bromo, methoxy, methyl, and protected amino groups. The reactivity of 2-naphthols was higher than that of 1-naphthols (Table 2, entries 1 and 2). When 1- or 2-naphthols containing substituent groups were treated with **2a** under the optimized conditions, the yields decreased remarkably (entries 3–6), with chloro-substituted naphthols gave higher yields



В

$\bigcirc$	OH + OSK	Catalyst Solvent, Temper	rature	J.	
1a 2a				3a	
Entry	Catalyst	Solvent	Temp (°C)	Yield <sup>b</sup> (%)	
1	-	MeCN	80	68	
2	-	DMSO	80	trace	
3	-	DMF	80	trace	
4	-	DCE	80	trace	
5	Cul	MeCN	80	73	
6	CuBr	MeCN	80	72	
7	CuCl	MeCN	80	76	
8	CuOAc	MeCN	80	78	
9	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	MeCN	80	85	
10 <sup>c</sup>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	MeCN	80	79	
11 <sup>d</sup>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	MeCN	80	93	
12 <sup>d</sup>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	MeCN	r.t.	39	
13 <sup>d</sup>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	MeCN	60	75	
14 <sup>d</sup>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	MeCN	100	78	
15 <sup>d</sup>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	MeCN	120	56	

<sup>a</sup> Reaction conditions: **1a** (0.3 mmol), **2a** (2.0 equiv), solvent (2 mL), catalyst (0.2 equiv), under air, 8 h.

Isolated yield

<sup>c</sup> 2a (1.5 equiv).

<sup>d</sup> **2a** (3.0 equiv).

than bromo-substituted naphthols. In addition, we found that the reactivity of phenols was lower than that of 1- or 2naphthols. The position of the substituent group had a marked effect on the reaction. For example, the reaction of 4-methoxyphenol gave a 68% yield of the acetate, whereas the 3-methoxyphenol gave a 56% yield (entries 7 and 8). Methylated phenols and 4-(dimethylamino)phenol gave only moderate yields of the corresponding acetates (entries 9–11).

Having successfully investigated the acetylation of naphthols and phenols, we further expanded the scope of the substrates to include anilines. Under the standard conditions with the copper catalyst, electron-rich anilines were compatible with this protocol and gave high yields of the corresponding amides (Table 3; Method A). In addition, while screening the conditions for this reaction, we found that it could be catalyzed by *t*--BuONO at room temperature, albeit with slightly lower yields (Table 3; Method B). The highest yield was obtained from the reaction of 4-methoxyaniline (Table 3, entry 1). Like the acetylation of 4and 3-substituted phenols, the reaction of 4-methylaniline gave a higher yield than that of 3-methylaniline (entries 2 and 3). Aniline gave N-phenylacetamide in yields of 77% and 72% by Methods A and B, respectively (entry 4). Notably, 4fluoroaniline also gave a high yield of the corresponding ac**Synlett** 

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etamide (entry 5). Interestingly, for 4-aminophenol as a substrate, the diacetylation product was obtained in moderate yield (entry 6). Other substituted anilines were tried under the two standard conditions, but the yields were relatively low (not shown). Attempts to apply the process to the acetylation of aliphatic amines or alcohols proved problematic for reasons that remain unclear.





Table 2 (continued)



<sup>a</sup> Reaction conditions: **1a–k** (0.5 mmol), **2a** (3.0 equiv), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (0.2 equiv), MeCN (3 mL), 80 °C, under air, 8 h. <sup>b</sup> Isolated yield.

To investigate the reaction mechanism, we performed a radical-trap experiment. When a stoichiometric amount of the radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was added to the reaction mixture under the standard reaction conditions, only a trace amount of product **3a** was detected. This result suggests that the reaction involves a free-radical process. On the basis of this results and reports in the literature, we propose a plausible mechanism for this reaction, as shown in Scheme 1. In the presence of copper catalyst and air atmosphere, potassium thioacetate readily forms the acetylsulfanyl radical **I**, which is then transformed into the key diacetyl disulfide (**II**) by a radical coupling reaction. The acetylation product is then was formed through nucleophilic attack on the electron-rich aniline or phenol.

In summary, we have described an acetylation of phenols and anilines with potassium thioacetate catalyzed by copper(II) acetate.<sup>13</sup> In addition, the acetylation of anilines proceeded at room temperature in moderate to high yields when *t*-BuONO was used as the catalyst. This simple procedure serves as an important complementary route to previous acetylation reactions due to certain advantages of this acetylating reagent, such as its low cost, easy available, stability, insensitivity to water and air, and ease of storage. However, this reaction also has some limitations, as it is only suitable for electron-rich phenols and anilines. Further studies to expand the substrate scope are currently underway in our laboratory.

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<sup>a</sup> Reaction conditions: Method A: **4a–e** (0.5 mmol), **2a** (3.0 equiv), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (0.2 equiv), MeCN (3 mL), 80 °C, under air, 8 h; Method B: **4a–e** (0.5 mmol), **2a** (2.0 equiv), *t*-BuONO (0.2 equiv), MeCN (3 mL), r.t., under air, 4 h.

<sup>b</sup> Isolated yield

<sup>c</sup> 2a (6.0 equiv)

<sup>d</sup> 2a (4.0 equiv).



Scheme 1 Possible mechanism

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## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611741.

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## (13) Acetylation of Anilines and Phenols with Potassium Thioacetate: General Procedure

The appropriate aniline or phenol (0.5 mmol), KSAc (3.0 equiv), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (0.2 equiv), and MeCN (3 mL) were added to a screw-capped vial under air, and the vial was placed in a temperature-controlled oil bath at 80 °C. When the reaction was complete (TLC), the vial was removed from the oil bath and allowed to cool to r.t. The solution was filtered through a short column of silica gel that was washed with EtOAc. The filtrate was concentrated under reduced pressure to give a crude product that was purified by flash column chromatography (silica gel, PE–EtOAc).

#### 2-Naphthyl Acetate (3a)

Creamy-white solid powder; yield: 86.5 mg (93%); mp 68–70 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.91–7.84 (m, 3 H), 7.61 (s, 1 H), 7.52 (t, *J* = 3.9 Hz, 2 H), 7.29 (t, *J* = 7.2 Hz, 1 H), 2.40 (s, 3 H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 169.8, 148.4, 133.8, 131.6, 129.5, 127.9, 127.7, 126.7, 125.8, 121.2, 118.6, 21.3.