

# Copper-Catalyzed Coupling of Oxime Acetates with Isothiocyanates: A Strategy for 2-Aminothiazoles

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#### **Supporting Information**

**ABSTRACT:** A new strategy for 2-aminothiazoles is developed via the copper-catalyzed coupling of oxime acetates with isothiocyanates. Various 4-substituted and 4,5-disubstituted 2-aminothiazoles were formed smoothly under mild reaction conditions. This process involved copper-catalyzed N–O bond cleavage, activation of vinyl sp<sup>2</sup> C–H bonds, and C–S/C–N bond formations. It is noteworthy that the oxime acetates were used not only as a substrate but also as a single oxidant.



n the past few decades, transition-metal-catalyzed oxidation reactions have been a good method for carbon-carbon and carbon-heteroatom bond formations.<sup>1</sup> However, the use of the external oxidants makes these reactions suffer from harsh reaction conditions, poor functional group tolerance, and the waste of the reduced external oxidant. To solve this problem, attention has shifted to the internal oxidants.<sup>2</sup> The reactions which utilize internal oxidants are redox-neutral and do not require external oxidants. While the  $N-N_{1}^{3}$   $N-S_{1}^{4}$  and N- $O^{5-7}$  bonds were all used as internal oxidants, the N–O bond is the most common. Narasaka et al. seminally studied palladium-catalyzed intramolecular Heck-type cyclization of oxime derivatives, and other groups recently reported palladium-catalyzed C-H functionalizations which use the N-O bond as the internal oxidant.<sup>5</sup> In addition, the N-O bond cleavage was also used as the oxidant in ruthenium- and rhodium-catalyzed reactions.<sup>6,7</sup> These reactions utilizing internal oxidants have many advantages, such as mild reaction conditions, high selectivity, and good functional group tolerance. Thus, it is meaningful and desirable to apply internal oxidants in more transition-metal-catalyzed oxidation coupling reactions.

The 2-aminothiazole motif has been widely used in medicinal chemistry.<sup>8</sup> Until now, one of the most common methods for the synthesis of 2-aminothiazoles has been the Hantzsch reaction, which uses  $\alpha$ -halocarbonyl compounds to couple with thioureas.<sup>9</sup> Recently, reactions directly starting from ketones and thioureas have been also reported for synthesis of 2aminothiazole.<sup>10</sup> However, they suffer from harsh reaction conditions, poor functional group tolerance, or limited starting materials. Therefore, it is desirable and challenging to develop more green reagents and new routes for 2-aminothiazoles. An oxime ester, which comes from the esterification of oxime, is cheap and readily available.<sup>11</sup> In recent years, we and other groups have found that oxime esters were good synthons for nitrogen-bearing heterocyclic compounds in the presence of a copper catalyst,<sup>12,13</sup> and oxime esters were used not only as substrates but also as oxidants. We have developed a series of methods for the synthesis of N-heterocycle compounds such as

pyrroles, imidazo[1,2-*a*]pyridines, pyrazoles, and pyridines via copper-catalyzed coupling reactions with oxime esters as the substrates (Scheme 1a–d).<sup>12</sup> Herein, we report a novel method

## Scheme 1. Our Previous Work and This Work



for 2-aminothiazoles via the copper-catalyzed oxidative coupling of oxime acetates with isothiocyanates using N-O bonds as the internal oxidant; thus, there is no need for additional oxidants (Scheme 1e).

At the start of our studies, we used acetophenone oxime acetate (1a) and phenyl isothiocyanate (2a) as models to screen bases, copper salts, and solvents, and the results are summarized in Table 1. Initial attempts were performed with a catalytic amount of CuI,  $K_2CO_3$  as base, and toluene as solvent under an air atmosphere. We were excited that the unpredicted product *N*,4-diphenylthiazol-2-amine (3aa) was obtained in

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Table 1. Optimization of Reaction Conditions<sup>a</sup>

N Ph 1a	∠OAc +	Ph   N=C=S 2a [Cu], bas toulene, 105	e Ph N 5°C S 3aa	∽NHPh
entry	[Cu]	base	solvent	yield <sup>b</sup> (%)
1	CuI	K <sub>2</sub> CO <sub>3</sub>	toluene	14
2	CuI	Na <sub>2</sub> SO <sub>3</sub>	toluene	23
3	CuI	NaHSO <sub>3</sub>	toluene	13
4	CuI	KO <sup>t</sup> Bu	toluene	43
5	CuI	DBu	toluene	15
6	CuI	Cs <sub>2</sub> CO <sub>3</sub>	toluene	84 (80)
7	CuI	-	toluene	n.d.
8	-	$Cs_2CO_3$	toluene	n.d.
9	CuCl	$Cs_2CO_3$	toluene	42
10	CuBr	$Cs_2CO_3$	toluene	79
11	$CuCl_2$	$Cs_2CO_3$	toluene	12
12	CuBr <sub>2</sub>	$Cs_2CO_3$	toluene	14
13	$Cu(OAc)_2$	$Cs_2CO_3$	toluene	69
14	$Cu(OTf)_2$	$Cs_2CO_3$	toluene	67
15	CuI	$Cs_2CO_3$	DMSO	n.d.
16	CuI	Cs <sub>2</sub> CO <sub>3</sub>	DMF	n.d.
17	CuI	Cs <sub>2</sub> CO <sub>3</sub>	1,4-dioxane	48
18 <sup>c</sup>	CuI	Cs <sub>2</sub> CO <sub>3</sub>	toluene	82

<sup>*a*</sup>Reaction conditions: unless otherwise noted, all reactions were performed with 1a (0.5 mmol), 2a (0.5 mmol), base (0.25 mmol), and [Cu] (20 mol %), in toluene (3 mL) at 105 °C under air for 8 h. <sup>*b*</sup>Determined by GC and dodecane as internal standard. Number in parentheses is yield of isolated product. <sup>*c*</sup>Under N<sub>2</sub> atmosphere.

14% GC yield (Table 1, entry 1). Various bases, such as Na<sub>2</sub>SO<sub>3</sub>, NaHSO<sub>3</sub>, KO<sup>t</sup>Bu, DBU, and Cs<sub>2</sub>CO<sub>3</sub>, were examined (entries 2-6). To our delight,  $Cs_2CO_3$  gave a satisfactory yield (84% GC yield and 80% isolated yield). Without a base or catalyst, there was no product detected (entries 7-8). Different copper salts such as CuCl, CuBr, CuCl<sub>2</sub>, CuBr<sub>2</sub>, Cu(OAc)<sub>2</sub>, and  $Cu(OTf)_2$  could also catalyze this reaction (entries 9–14). When we used DMSO and DMF as solvents, the desired product was not detected and acetophenone oxime acetate was found to be decomposed into acetophenone oxime and acetophenone (entries 15-16). However, we could obtain a moderate yield when using 1,4-dioxane as solvent (entry 17). When the reaction was performed under a N<sub>2</sub> atmosphere, the result was the same as that under an air atmosphere (entry 18). In order to simplify the operation, we elected to carry out our process under an air atmosphere. Thus, the optimal catalytic system for this copper-catalyzed oxidative coupling reaction was as follows: 1a (0.5 mmol), 2a (0.5 mmol), CuI (20 mol %), and  $Cs_2CO_3$  (0.25 mmol) in toluene (3 mL) at 105 °C under air for 8 h.

With the optimized reaction conditions in hand, the generality of this copper-catalyzed oxidative coupling of oxime acetates with isothiocyanates was examined. The scope of the oxime acetates was first explored by the adoption of phenyl isothiocyanate as the coupling partner, and the results are summarized in Scheme 2. Both electron-rich (H, 1a; CH<sub>3</sub>, 1b; OMe, 1f) and electron-poor (halogen, 1c-e) *para*-substituted acetophenone oxime acetates participated well in this reaction, and the desired products were formed in good yields. In addition, the substrates with a fluoro, chloro, bromo group at the *meta*- or *ortho*-position could also react smoothly to afford the corresponding products with good to excellent yields (3ga-3la). In general, acetophenone oxime acetates with





<sup>*a*</sup>The reactions were carried out at 105 °C using 1 (0.5 mmol), **2a** (0.5 mmol), CuI (20 mol %), and  $Cs_2CO_3$  (0.25 mmol) in toluene (3 mL) under air for 8 h. Yields refer to the isolated yields.

an electron-donating group showed higher reactivity than those with an electron-withdrawing group. Unfortunately, a strong electron-withdrawing group such as nitro was not applicable in this transformation. It is worth noting that the disubstituted acetophenone oxime acetates were a suitable substrate, and the corresponding products were formed in 81% and 70% yields, respectively (**3ma**, **3na**). Notably, a heteroaryl-bearing oxime acetate was also compatible for this transformation and transferred to the corresponding product in 75% yield (**3oa**). More importantly, the strategy was also available for the construction of 4,5-disubstituted 2-aminothiazoles in good yields (**3pa-3wa**).

Next, the scope of isothiocyanates was examined for this reaction (Scheme 3). For various *para*-substituted phenyl isothiocyanates with electron-donating or -withdrawing substituents on the aromatic ring, the reactions proceeded smoothly to afford the desired products **3ab**-**3af** in good yields. When 3-methylphenyl isothiocyanate was used, product **3ag** was isolated in 77% yield. It is worth mentioning that the annulation reaction could be expanded to alkyl and benzyl isothiocyanates, and the corresponding products could be formed in 90%, 73%, and 85% yields, respectively (**3ah**-**3aj**).

To gain more insight into the reaction mechanism, we added the radical scavenger TEMPO or BHT to our standard reaction [eqs 1 and 2]. When TEMPO was added, the reaction system was very complex and no product was detected. In addition, acetophenone was obtained in 18% yield and acetophenone oxime acetate was recovered in 11% yield [eq 1]. When BHT was added, the conditions were similar to the case with TEMPO; acetophenone was obtained in 10% yield and acetophenone oxime acetate was recovered in 35% yield [eq 2]. When phenyl isocyanate was added to the reaction, the corresponding product 4 was not detected [eq 3].

Based on previous works on copper-catalyzed transformation of oxime esters and our control experiment, a possible mechanism is proposed in Scheme 4.<sup>12–16</sup> First, iminium radical **A** was produced via reduction by  $\text{Cu}^{\text{I},12-14}$  The freeScheme 3. Cu(I)-Catalyzed Synthesis of 2-Aminothiazoles from Acetophenone Oxime Acetate and Various Isothiocyanates<sup>a</sup>



<sup>*a*</sup>The reactions were carried out at 105 °C using 1a (0.5 mmol), 2 (0.5 mmol), CuI (20 mol %), and  $Cs_2CO_3$  (0.25 mmol) in toluene (3 mL) under air for 8 h. Yields refer to the isolated yields.



Scheme 4. Possible Catalytic Cycle



radical addition of iminium radical **A** to phenyl isothiocyanate formed the intermediate **B**, which isomerized to intermediate **C**. Subsequently, intramolecular free-radical addition occurs to construct a new C–S bond to afford intermediate **D** (path a).<sup>15</sup> It is also possible that the intermediate **D** is generated by addition of carbon radical **F** to the sulfur atom of phenyl isothiocyanate, followed by intramolecular radical cyclization

and isomerization (path b).<sup>16</sup> Subsequently, the intermediate **D** was oxidized by  $Cu^{II}$  to give the intermediate **E**. Finally, the desired product **3aa** was obtained by deprotonation and the resulting acid was neutralized by the base.

In summary, an efficient and external-oxidant-free 2-aminothiazole synthesis from copper-catalyzed oxidative coupling of oxime acetates with isothiocyanates has been developed. Importantly, the reaction was accomplished through N–O bond cleavage, and new C–S/C–N bond formations, along with the activation of vinyl sp<sup>2</sup> C–H bonds under mild conditions. Various 4- and 4,5-substituted 2-aminothiazoles were formed in good yields. Further studies on this topic are currently underway in our laboratory.

# ASSOCIATED CONTENT

### **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.5b03188.

Typical experimental procedure and characterization for all products (PDF)

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#### Notes

The authors declare no competing financial interest.

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