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Copper-Catalyzed Synthesis of Thiazol-2-yl Ethers from Oxime Acetates and Xanthates under Redox-Neutral Conditions

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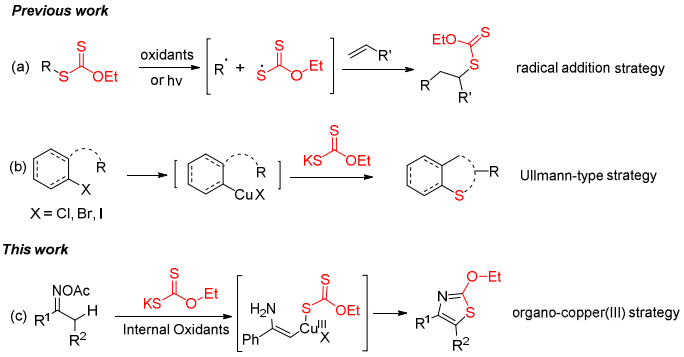
A novel copper-catalyzed annulation of oxime acetates and xanthates for the synthesis of thiazol-2-yl ethers with remarkable regioselectivity has been developed. Various oxime acetates, whether derived from aryl ketones or alkyl ketones, or natural product cores are suitable for this conversion. The unique dihydrothiazoles were also obtained when both reaction sites are methine. Mechanistic studies indicated that imino copper(III) intermediates were involved. In addition, this protocol proceeded under redox-neutral conditions and did not need for additives or ligands.

Thiazole skeletons are versatile privileged motifs widely found in natural products[1] and exhibit a wide range of biological activities.[2] Many natural products such as Apratoxins, Luciferin, Piscibactin, Dolastatin E, Mirabazole, Tantazoles, Vitamin B1, Epothilones, Thiostrepton and some of accepted drugs included dasatinib, Ritonavir, nizatidine and fentiazac contain thiazole moieties.[3,4] Further, they have been used as synthetic ligands, cosmetic sunscreens and also applied to various biological evaluations.[5] Many practical method including some of our group[7a,7b] have been reported for the synthesis of thiazoles, especially 2-aminothiazoles.[6,7] However, the direct synthesis of thiazol-2-yl ethers remains greatly underrepresented in the literature. In this regard, only few methods are still limited to halogenated thiazoles ring or α-haloketones as prefunctionalized substrates.[5c,5d] So far, it is significant to develop more practical and alternative methods for the construction of thiazol-2-yls from available raw materials.

C-S bond as a basic chemical bond, its cleavage and formation play crucial role in chemical reaction. During the past decades, xanthate derivatives as an important sulfur-containing compound, are widely used in organic synthesis, especially in radical addition reactions.[8] In this context, many kinds of radical reactions of xanthate-based on the degenerative exchange of a thiocarbonyl thio group have been demonstrated as powerful tools for the construction of C-C bonds[9] and C-S bonds[10] (Scheme 1a). Noteworthy, Sekar and other chemists have reported several examples triggered by Ullmann-type reaction with potassium xanthates (Scheme 1b).[11] However, the use of prefunctionalized materials is relatively uneconomical and environmentally unfriendly. Therefore, the developing of more reaction types of xanthates for the preparation of sulfur-containing molecules is highly desirable.



Scheme 1. The utilization of thio part of thiocarbonyl for xanthate derivatives

Oxime acetates as an internal oxidant have been found to be versatile building blocks wildly applied in the field of transition metal-catalyzed reactions due to their unique properties,[12-14] especially under copper catalysis. Based on our previous work on oxime derivatives[7a,7b,14] herein, we describe a novel [3+2] annulation of oxime acetates with xanthates via organo-copper(III) strategy (Scheme 1c). This transformation provides a simple way for the preparation of various thiazol-2-yl ethers with good stereoselectivity.

After extensive screening of different parameters, the optimal reaction conditions were determined (see the Supporting Information for details). Then the substrate scope of aryl oxime acetates was investigated and the results were summarized in Table 1. Firstly, a series of *para*-substituted acetophenone oxime acetates, including electron-donating groups (Me, Et, OMe, SMe) and

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Electronic supplementary information (ESI) available: Experimental section, characterization of all compounds, and copies of ^{1}H and ^{13}C NMR spectra for selected compounds. For ESI and other electronic format See DOI:10.1039/x0xx00000x

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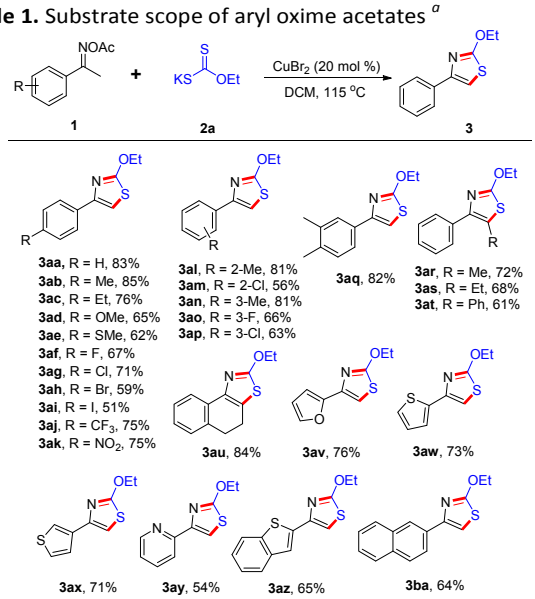
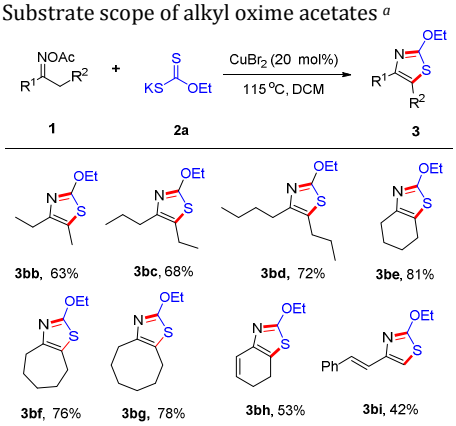
electron-withdrawing groups (F, Cl, Br, I, CF_3, NO_2) were converted into the corresponding thiazol-2-yl ethers (**3ab-3ak**). Furthermore, *ortho*, *meta*-substituted and *poly*-substituted acetophenone oxime acetates were able to give the desired products in moderate to good yields (**3al**-**3aq**). Moreover, oxime acetates derived from other aromatic ketones such as propiophenone, butyrophenone, 1,2-diphenylethan-1-one and 3,4-dihydronaphthalen-1(2*H*)-one could be accessed through this route to generate the annulation products in good yields (**3ar**-**3au**). In addition, the heteroarene oxime acetates were compatible with this transformation (**3av**-**3ay**). When 1-(benzo[*b*]thiophen-2-yl)ethan-1-one and 1-acetylnaphthalene oxime acetate were used as the substrate, **3az** and **3ba** could be isolated in 65% and 64% yields, respectively.

Table 1. Substrate scope of aryl oxime acetates [a]



[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.36 mmol), $CuBr_2$ (0.06 mmol), in 2.0 mL DCM at 115 °C for 6 h. Isolated yield.

Table 2. Substrate scope of alkyl oxime acetates [a]

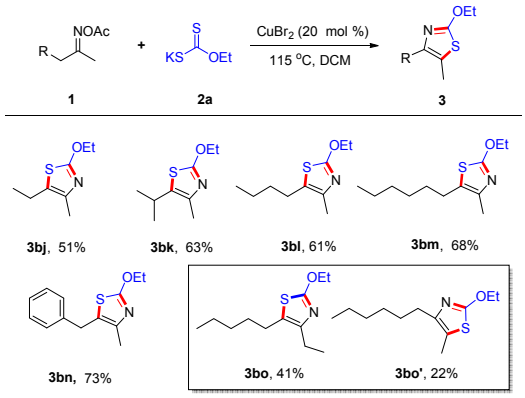


[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), $CuBr_2$ (0.04 mmol), in 2.0 mL DCM at 115 °C for 6 h. Isolated yield.

Next, we examined the scope of aliphatic oxime acetates (Table 2). To our delight, a large number of aliphatic oxime acetates are compatible with this transformation. Different chain ketoxime esters, for example, pentan-3-one *O*-acetyl oxime, heptan-4-one *O*-acetyl oxime and nonan-5-one *O*-acetyl oxime could react with **2a** smoothly and afforded the corresponding products in good yields (**3bb**-**3bd**). In addition, the cyclic alkyl oxime esters were also compatible with this reaction, providing the polycyclic products in moderate to good yields (**3be**-**3bg**). Additionally, oxime acetates substituted with alkenyl groups such as cyclohex-2-en-1-one *O*-acetyl oxime and 4-phenylbut-3-en-2-one *O*-acetyl oxime, were smoothly transformed into the corresponding alkenyl products in 53% and 42% yields, respectively (**3bh**, **3bi**).

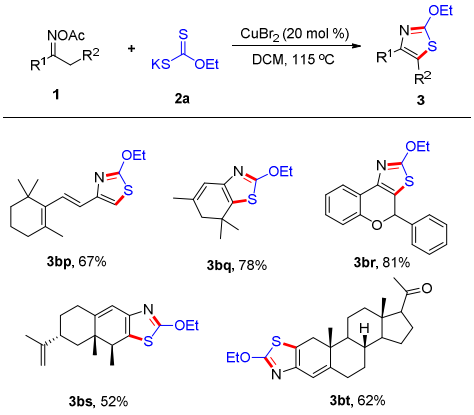
When oxime acetates bore different two reaction sites (C(sp^3)-H bonds) at the *α* position of the C=N group, the major product is the one that has the fewest hydrogen substituents. In particular, when one of them is methyl, only the single product is present (**3bj**-**3bn**). And when both of them are methylenes, there will be different products appear at a certain rate (**3bo** and **3bo'**).

Table 3. The substrate scope and stereoselectivity of oxime acetates [a]



[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), $CuBr_2$ (0.04 mmol), in 2.0 mL DCM at 115 °C for 6 h. Isolated yield.

Table 4. Synthesis of thiazol-2-yl ether derivatives derived from natural product cores [a]



[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), $CuBr_2$ (0.04 mmol), in 2.0 mL DCM at 115 °C for 6 h. Isolated yield.

To further demonstrate the synthetic utility of this strategy, the structure modification was also applied to some natural product cores. As shown in Table 4, oxime acetates derived from β-ionone, Isophorone, Flavanone and Nootkatone smoothly participated in

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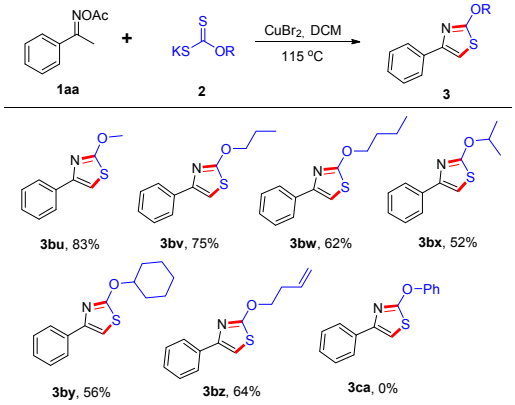
the transformation, affording the thiazide-skeleton molecules in moderate to good yields (**3bp-3bs**). In addition, when oxime acetate derived from Progesterone was used as the substrate, the cyclization reaction only reacts at one end of the six-membered ring and a single product **3bt** was obtained in 62% yield, which might be due to the preference to enolization or the steric hindrance.

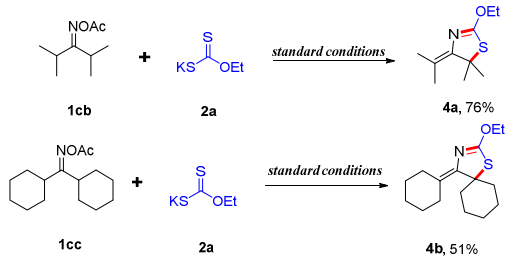
Furthermore, the substrate scope with regard to xanthates was evaluated (Table 5). Different straight chain alkyl potassium xanthates with **1aa** were reacted smoothly, and the corresponding products could be obtained in moderate yields (**3bu–3bw**). In addition, branched alkyl potassium xanthates could also react smoothly under the standard conditions (**3bx**, **3by**). Moreover, potassium xanthate with alkenyl was also compatible in this reaction, affording the desired product **3bz** in 64% yield. Regrettably, the aryl potassium xanthate did not react in this strategy (**3ca**).

Table 5. Substrate scope of potassium xanthates [a]



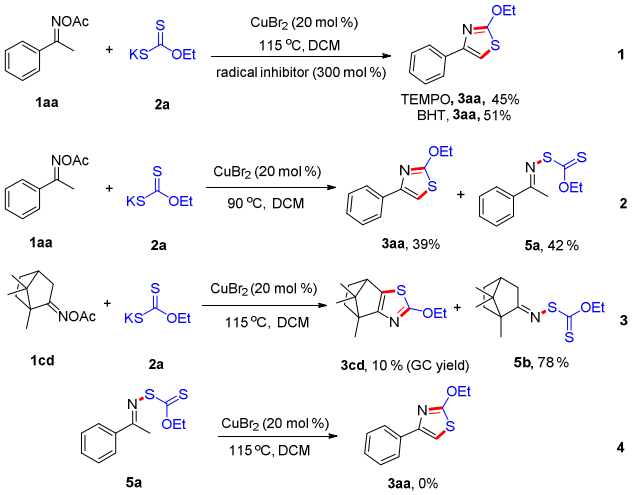
[a] Reaction conditions: **1aa** (0.2 mmol), **2** (0.3 mmol), $CuBr_2$ (0.04 mmol), in 2.0 mL DCM at 115 °C for 6 h. Isolated yield.

In addition, when oxime acetates bearing two methines at *α* position of the C=N group reacted under the standard conditions, the corresponding dihydrothiazoles were obtained (Scheme 2). For example, using oxime acetate **1cb** as a substrate, the reaction proceeded smoothly and the corresponding product **4a** was obtained in 76% yield. Similar results were observed when oxime acetate **1cc** was used under the standard condition, the desired product **4b** was achieved in 51% yield.



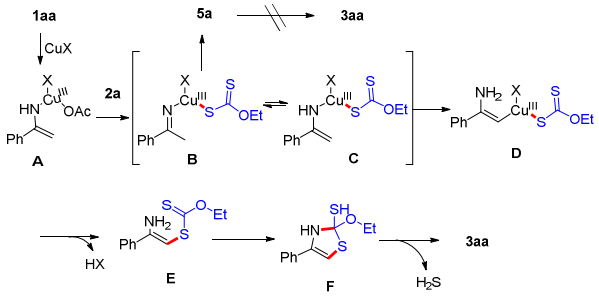
Scheme 2. The synthesis of dihydrothiazoles **4**

To gain more insight into the reaction mechanism, several experiments were performed in Scheme 3. First, when TEMPO and BHT were added, this conversion was not inhibited completely, showing that the generation of radicals should not be involved [eq. 1]. When reducing the temperature, **5a** was obtained in 42% yield, which may come from the reductive elimination of organo-copper(III) intermediates [eq. 2]. Moreover, the treatment of **2a** with large steric substrate camphorone oxime acetate under the standard conditions led to the product **5b** in 78% yield [eq. 3]. This result indicated that large steric hindrance inhibited the isomerization of imino copper(III) intermediates. In addition, the treatment of **5a** under the standard conditions, **3aa** could not be obtained [eq. 4].



Scheme 3. Control experiments

On the basis of these experimental results as well as previous works,[12-14] a tentative mechanism involved imino copper(III) intermediates is proposed in Scheme 4. First, intermediate **A** is formed by oxidative addition of the N-O bond of **1aa** to copper(I).[7b, 13e, 14a] Coordination of potassium xanthates to **A** gives intermediate **B** and simultaneously releases KOAc. Tautomerization and activation of the vinyl C-H bonds provides copper(III) intermediate **D**, which would transform to **E** and release copper(I) catalyst via the reductive elimination process. And intramolecular cyclization of **E** generates intermediate **F**. Finally, hydrogen sulfide was removed at high temperature and gave the product **3**. In addition, when the reaction temperature was reduced or the substrate steric hindrance was increased greatly, by-product **5a** tended to be produced via direct reductive elimination of intermediate **C**.



Scheme 4. Proposed mechanism

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In summary, a practical copper-catalyzed [3+2] annulation for the synthesis of thiazol-2-yl ethers has been reported from oxime acetates with xanthates. Excellent functional group tolerance of oxime acetates derived from aryl ketones, alkyl ketones makes this reaction practical. Furthermore, this transformation provided a efficient strategy for the structure modification of natural product. Experiments showed that the regioisomeric preferences may be relating to the preference for the site of enolization and the one with fewest hydrogen substituents was the major product. Unique dihydrothiazole product also could be obtained from the specific substrate. Moreover, the preliminary mechanism studies showed that this strategy was involved a copper(I)-copper(III) catalytic cycle with oxime acetates as an internal oxidant.

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Conflicts of interest

There are no conflicts to declare.

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