ORGANIC LETTERS

2013
Vol. 15, No. 17
4600–4603

# Cu-Catalyzed Cross-Dehydrogenative Coupling Reactions of (Benzo)thiazoles with Cyclic Ethers

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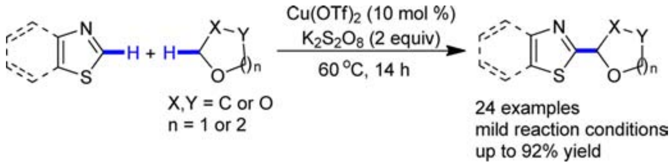
**Received August 5, 2013**

## ABSTRACT



**Copper-catalyzed cross-dehydrogenative coupling (CDC) reactions of (benzo)thiazoles with cyclic ethers were developed under mild conditions. In particular, the formation of C−C bonds via the CDC reactions between non-benzo-fused azoles and ethers are reported for the first time. In addition, the acetals, known as the masked 2-thiazolecarboxaldehydes, could be successfully obtained by this CDC reaction. The preliminary mechanism and supportive DFT calculations are discussed as well.**

Azoles, especially (benzo)thiazoles, are widespread in various natural products[1] from agriculture and pharmaceutical agents to material sciences.[2] More recently, the cleavage and functionalization of C−H bonds in azoles has attracted considerable attention because of their potential possibility to transform into other valuable compounds.[3] In the past decades, inspiring progress on transition-metal-catalyzed reactions of azoles has been made,[4] where the direct cross-dehydrogenative coupling (CDC) reactions were of particular importance[5] because the introduction of oriented and activated functional groups in azoles were avoided, making synthetic routes shorter and more atom-economical.[6]

Numerous examples of C−C, C−N, and C−P bond formations of azoles by CDC reactions have been reported, such as arylation or aroylation of azoles with arenes[7] and aldehydes;[8] the CDC reactions of azoles with azoles;[9] N-alkylation, N-arylation, amidation, or amination of azoles with dimethylacetamide, benzylamine, secondary amine, and formamides;[10] and phosphonation of azoles with phosphites.[11] In the CDC reactions, transition metals, especially noble metals, were widely used, but the

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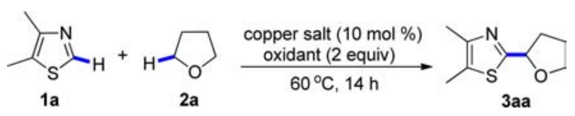
10.1021/ol4022113

application of inexpensive metals, such as copper and iron, remains limited and is still a big challenge.

Tetrahydrofuran (THF) and dioxane are important chemical raw materials and usually used as common solvents in various chemical reactions for their chemical inertness.[12] Thus, there were some inherent difficulties in the activation of THF and dioxane, and only a few examples were reported based on the activation of THF and dioxane. For example, Wan[13] and Reddy[14] reported the formation of C–O bond via the activation of C–H bonds of cyclic ethers. Li and co-workers[15] reported the formation of C–N bonds catalyzed by Fe. However, the direct formation of C–C bonds between azoles and cyclic ethers was very rarely reported, and the only example was reported by Wang and co-workers,[16] in which the C–C bonds between benzoazoles (including benzoxazole, benzothiazole, and benzimidazole) and ethers were formed via the CDC reactions. In particular, there is no reported example on the formation of the C–C bonds between ethers and non-benzo-fused azoles via the CDC reactions for the following possible reasons: (a) non-benzo-fused azoles are more $\pi$-electron-deficient and show weaker acidity than benzoazoles;[17] (b) non-benzo-fused azoles may generate more regioisomeric products with more active sites than benzoazoles; and (c) for non-benzo-fused azoles, oxidative homocoupling more easily occurred than CDC reaction.[18] Followed by our recent work on Cu-catalyzed direct C–H bond activation,[19] here we report a novel Cu-catalyzed CDC reaction between (benzo)thiazoles and cyclic ethers, especially, to the best of our knowledge, with the first example of the formation of C–C bonds between non-benzo-fused azoles and cyclic ethers so far. More interestingly, while dioxolane was used as a special cyclic ether in this CDC reaction, the acetals of 2-thiazolecarboxaldehydes were also obtained successfully, which provided an aldehyde-free synthetic protocol for the acetals of 2-thiazolecarboxaldehydes.

In our initial study, 4,5-dimethylthiazole (**1a**) and THF (**2a**) were selected to test the CDC reactions. As shown in Table 1, up to 17 types of simple copper salts were tested (entries 1–17), where all the monovalence copper salts (CuCl, CuBr, CuI, CuCN, and $Cu_2O$) failed to obtain any product, and in the case of divalent copper salts ($CuSO_4 \cdot 5H_2O$, $Cu(acac)_2$, and CuO), the corresponding products were obtained with low yields. However, 80% and 82% of yields were obtained when $Cu(OTf)_2$ and $Cu(ClO_4)_2$ were used, respectively (Table 1, entries 12 and 17). Although $Cu(ClO_4)_2$ afforded a slightly higher yield than $Cu(OTf)_2$, we prefer $Cu(OTf)_2$ as the optimal catalyst, considering the safety of large-scale production. Next, the oxidant effect in this reaction was investigated, and more than 10 oxidants were tested (Table 1, entries 12 and 18–27), in which $K_2S_2O_8$ afforded the highest yield. In addition, we also found that inert gas was favorable to this

**Table 1.** Cu-Catalyzed CDC Reactions of Thiazole with THF[a]



| entry | copper salts | oxidants | yield[b] (%) |
|---|---|---|---|
| 1 | CuCl | $K_2S_2O_8$ | 0 |
| 2 | CuBr | $K_2S_2O_8$ | 0 |
| 3 | CuI | $K_2S_2O_8$ | trace |
| 4 | CuCN | $K_2S_2O_8$ | 0 |
| 5 | $CuBr_2$ | $K_2S_2O_8$ | trace |
| 6 | $CuCl_2$ | $K_2S_2O_8$ | trace |
| 7 | $CuCl_2 \cdot 2H_2O$ | $K_2S_2O_8$ | trace |
| 8 | $CuSO_4 \cdot 5H_2O$ | $K_2S_2O_8$ | 30 |
| 9 | $Cu(OAc)_2$ | $K_2S_2O_8$ | 0 |
| 10 | $Cu(OAc)_2 \cdot H_2O$ | $K_2S_2O_8$ | 0 |
| 11 | $Cu(acac)_2$ | $K_2S_2O_8$ | 20 |
| 12 | $Cu(OTf)_2$ | $K_2S_2O_8$ | 80 |
| 13 | $Cu(OH)_2$ | $K_2S_2O_8$ | trace |
| 14 | Cu | $K_2S_2O_8$ | 0 |
| 15 | CuO | $K_2S_2O_8$ | 25 |
| 16 | $Cu_2O$ | $K_2S_2O_8$ | 0 |
| 17 | $Cu(ClO_4)_2$ | $K_2S_2O_8$ | 82 |
| 18 | $Cu(OTf)_2$ | $Ag_2CO_3$ | 0 |
| 19[c] | $Cu(OTf)_2$ | TBHP | 62 |
| 20 | $Cu(OTf)_2$ | $Ag_2O$ | 0 |
| 21 | $Cu(OTf)_2$ | Oxone | 55 |
| 22 | $Cu(OTf)_2$ | BQ | 0 |
| 23 | $Cu(OTf)_2$ | $H_2O_2$ | 0 |
| 24 | $Cu(OTf)_2$ | Air | 0 |
| 25 | $Cu(OTf)_2$ | *m*-CPBA | 0 |
| 26[d] | $Cu(OTf)_2$ | $O_2$ | 0 |
| 27 | $Cu(OTf)_2$ | DDQ | 0 |
| 28[e] | $Cu(OTf)_2$ | $K_2S_2O_8$ | 86 |
| 29[d] | $Cu(OTf)_2$ | $K_2S_2O_8$ | 45 |

[a] Unless otherwise indicated, a mixture of **1a** (0.5 mmol), copper salt (10 mol %), and oxidant (2 equiv) in THF (2 mL) was stirred at 60 °C for 14 h under air. [b] Yield of isolated **3aa**. [c] 70% in water. [d] $O_2$ balloon was used. [e] Under $N_2$ atmosphere.

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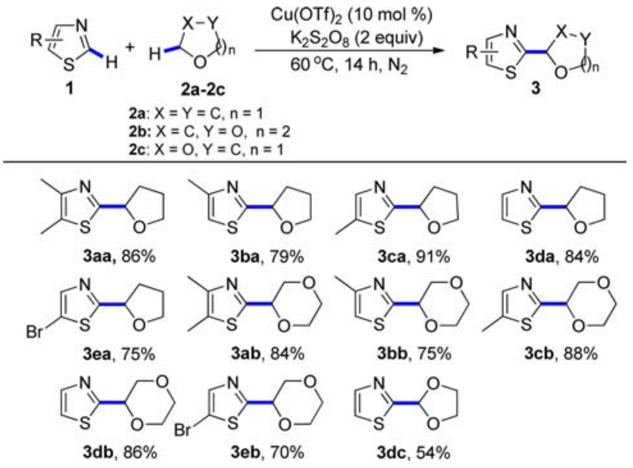
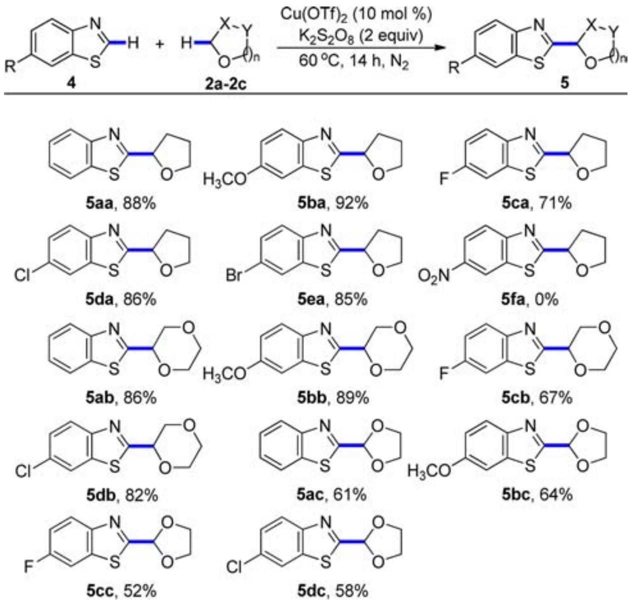
**Scheme 1.** Cu-Catalyzed CDC Reactions of Thiazoles with Ethers[a]



[a] The reaction was performed with **1** (0.5 mmol), $K_2S_2O_8$ (2.0 equiv), and $Cu(OTf)_2$ (10 mol %) in 2 mL of ether (**2**) under $N_2$ at 60 °C for 14 h. Yields refer to isolated yields.

**Scheme 2.** Cu-Catalyzed CDC Reactions of Benzothiazoles with Ethers[a]



[a] The reaction was performed with **4** (0.5 mmol), $K_2S_2O_8$ (2.0 equiv), and $Cu(OTf)_2$ (10 mol %) in 2 mL of ether (**2**) under $N_2$ at 60 °C for 14 h. Yields refer to isolated yields.

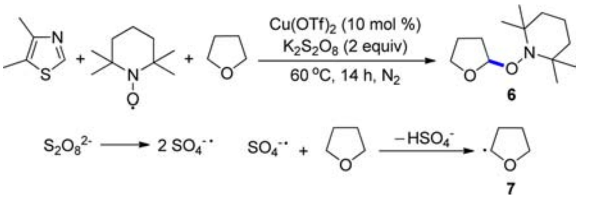
reaction, the yield was improved to 86% when the reaction was carried out under an atmosphere of dry nitrogen (Table 1, entry 28).

Subsequently, we explored the effects of reaction temperature, Cu-catalyst loading, and oxidant loading, respectively (see the Supporting Information). The reaction did not occur at ambient temperature (approximately 25 °C), and the yield of the reaction increased when the temperature was raised to 60 °C, whereas the yield did not increase when the temperature reached to 100 °C from 60 °C. Moreover, we also found that no product was obtained in the absence of the Cu catalyst, and when the $Cu(OTf)_2$ catalyst loading was reduced from 10 to 5 mol %, the yield was lowered from 86% to 62%. But when the $Cu(OTf)_2$ loading was raised to 15 mol %, the yield did not increase obviously. Next, under the above-mentioned conditions, the effect of oxidant loading was investigated. Finally, the addition of additive ligands (TMEDA, DMEDA, 2,2′-bipyridyl, and phen) and other solvents (DMF, $CH_3CN$, DCE, toluene, and hexane) were found to be ineffective to improve the yield. The above experiments clearly demonstrated that the optimized conditions for the CDC reaction of 4,5-dimethylthiazole and THF were shown as follows: $Cu(OTf)_2$ (10 mol %) and $K_2S_2O_8$ (2 equiv) in THF (2 mL) at 60 °C under $N_2$ for 14 h.

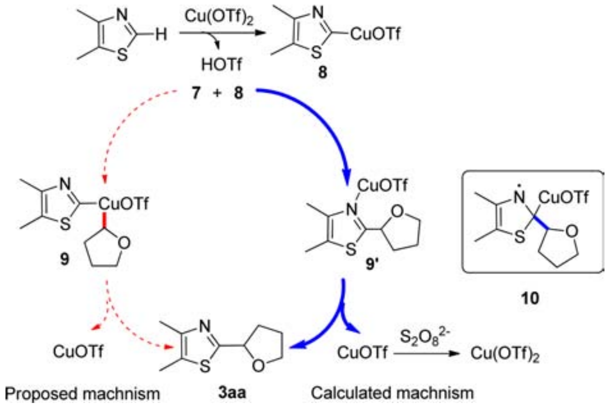
Next, as shown in Scheme 1, various thiazoles **1** were reacted with three types of cyclic ethers (**2a**−**c**), and the corresponding products **3** were obtained in moderate to excellent yields. It was noteworthy that the reactivity of 5-methylthiazole was much better than 4-methylthiazole (**3ca** vs **3ba**; **3cb** vs **3bb**). We also found electron-rich thiazoles gave slightly higher yields than electron-deficient ones (**3ca** vs **3ea**; **3cb** vs **3eb**). Interestingly, the CDC reaction could smoothly occur with dioxolane as the cyclic ether, where the corresponding products **3dc** could be achieved with the 54% yield and it could be transformed to 2-thiazolecarboxaldehyde by simple hydrolysis. We then tried to extend non-benzo-fused thiazoles **1** to benzothiazoles **4** in the CDC reaction. As displayed in Scheme 2, the desired products **5** were obtained in satisfactory yields under the same conditions, and the substituent group on benzothiazoles **4** caused a certain influence on the product yield. From the results listed in Scheme 2, we could find that 6-methoxybenzothiazole (**5ba**) afforded a much higher yield than benzothiazole with a halide substituent group (**5ca**, **5da**, **5ea**). Among the benzothiazoles with various electron-withdrawing substituents, 6-fluorobenzothiazole afforded the corresponding products with the lowest yields (Scheme 2, **5ca**, **5cb**, **5cc**). However, in the case of more electron-deficient 6-nitrobenzothiazole and THF, no desired product was found. The scope of 1,3-dioxolane with various benzothiazole **4** were also screened, and all these examples gave the corresponding acetals in acceptable yields (Scheme 2, **5ac**−**dc**).

To understand the mechanism of this CDC reaction, TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl), as a radical-trapping reagent, was added into the reaction system to investigate the intermediates under the optimized conditions. No desired product **3aa** was found upon addtion of TEMPO, whereas the TEMPO−THF adduct **6** was detected (Scheme 3). Moreover, neither **3aa** nor **6** was found with the addtion of TEMPO but without the presence of the oxidant $K_2S_2O_8$. Therefore, radical intermediate **7** might be formed through a dehydrogenation of THF facilitated by sulfate radical anion that was produced from the heated potassium peroxydisulfate.[20] The possible catalytic cycle was then initially proposed in

**Scheme 3.** Mechanistic Consideration



**Scheme 4.** Possible Mechanism for Cu-Catalyzed CDC Reactions between **1a** and THF



Scheme 4 (left side, red dashed line) according to the literature.[17,21] First, organocopper species **8** was formed by a CMD process,[17] and then **9** was generated from organocopper species **8** with the radical intermediate **7**. Finally, the desired CDC reaction product **3aa** was obtained by a reductive elimination from Cu(III)−aryl species **9**.

In order to further verify the above proposed mechanism, we performed density functional calculations. First, two stable configurations of **8** were generated (Figure 1a), where the tetradentate copper complex (left) was calculated to be 0.7 kJ/mol more stable than the bidentate one (right). Next, the structure of species **9** was optimized (Figure 1b, left), in which the Cu atom was coordinated to the C2 atom (in thiazole) and the O atom (in OTf), and the corresponding distances were 1.893 and 1.916 Å, respectively. The distance between Cu and the radical C in **7** was 2.380 Å. Our calculations indicated that one of H atoms of species **7** could easily transfer to the N atom, forming the H-transferred **9** (Figure 1b, middle). In H-transferred **9**, the Cu−C (THF) length was 3.799 Å, showing that there was no any strong interaction between them. But when the radical intermediate **7** was set to attack the C2 in **8**, the species **9′** was formed (Scheme 4, right side, blue solid line), and its energy was 250 and 143 kJ/mol lower than the energy of species **9** and H-transferred **9**, respectively, which suggested that the species **9′** can be thermodynamically formed much more easily than **9** and H-transferred **9**. These results demonstrated that the intermediate to generate **3aa** was very likely to be **9′**. Presumably, the initial intermediate might be **10** generated by the addition of **7** to C═N bond in **8**,[22] which undergo the intramolecular radical elimination to generate **9′**, and CuOTf eliminated from **9′** was further oxidized to Cu(OTf)$_2$ by potassium peroxydisulphate to continue the catalytic cycle. It was also well understood that no less than 2 equiv of potassium peroxydisulfate was necessary to complete the reaction.

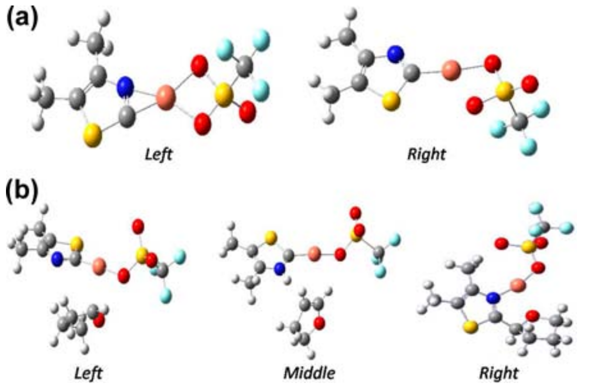


**Figure 1.** (a) (Left) tetradentate copper. (Right) bidentate copper. (b) Molecular structures of **9** (left), H-transferred **9** (middle), and **9′** (right).

In summary, an efficient copper-catalyzed method for cross-dehydrogenative coupling reactions of (benzo)-thiazoles with cyclic ethers was developed. This protocol provided not only a new avenue to form new C−C bonds between azoles, especially non-benzo-fused azoles, and inactive ethers but also an aldehyde-free synthesis for the acetals. Further research will focus on the more detailed mechanism and the formation of the C−C bonds between other azoles and acyclic ethers by CDC reactions.

**Acknowledgment.** We gratefully acknowledge financial support from the National Basic Research Program of China (2011CB808600) and the National Natural Science Foundation of China (Nos. 21102073, 21072093, and 20932004).

**Supporting Information Available.** Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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