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Copper-Catalyzed Activation of Disulfides as a Key Step in the Synthesis of Benzothiazole Moieties

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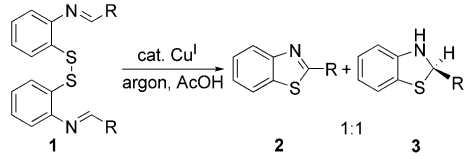
A convenient synthesis of substituted benzothiazoles has been accomplished by way of a copper catalyzed reaction of aromatic disulfide amines and aldehydes. The process, which involves copper catalyzed activation of disulfide functionality, proceeds in a tandem fashion via C–H bond activation, followed by aerobic oxidation of a resulting dihydrobenzothiazole intermediate. The scope and limitations of the reaction are demonstrated on a variety of substrates.

Introduction

Molecules featuring the benzothiazole structural motif play a key part in a wide variety of chemistries. Their diverse functions range from electron transfer facilitation in the firefly luciferine cycle[1] through antitumor[2] and antidiabetic activity[3] to Alzheimer disease tracer[4] and anticancer agent in pharmaceutical chemistry.[5] Their pharmaco chemistry in particular has witnessed renewed interest in the past couple of years,[2–5] which consequently secured an assortment of various synthetic methods for their preparation, including, for example, direct arylation of benzothiazoles, oxidative or metal-mediated cyclization of thioformanilides etc.[6]

Results and Discussion

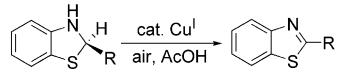
Here, we would like to present an additional, highly convenient method that allows for the preparation of functionalized benzothiazole species under mild, neutral reaction conditions from easily accessible substrates. The centerpiece of the method is the interaction between a disulfide moiety and a thiophilic metal – an interaction that enjoys growing attention in synthetic organic chemistry and biological chemistry alike.[7] In our previous work, we examined the origin of the above chemistry in the Cu-catalyzed intramolecular oxidation of imines by disulfides under anaerobic conditions.[8] It was found that the substrate **1** smoothly transformed, under the above conditions, into the products **2** and **3** in 1:1 ratio, and, based on our experiments, corroborated by the gas-phase data, a concise mechanism of the transformation was suggested, invloving the C–H bond activation as the rate-limiting step (see Scheme 1).



1 **2** **3**

Scheme 1. Cu-assisted S–S bond scission.

In order to utilize this novel metal-catalyzed process for the synthesis of benzothiazoles, dihydrobenzothiazole **3** was treated with air in the presence of a copper catalyst (Scheme 2). The cursory experiment resulted in quantitative conversion of the compound **3** into the benzothiazole product **2**.

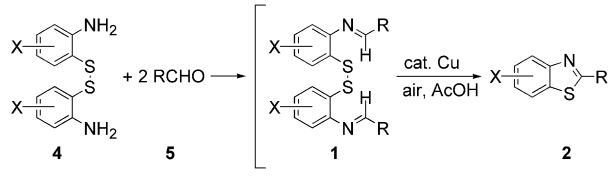


3 **2**

Scheme 2. Aerobic oxidation of dihydrobenzothiazole.

Connecting both, anaerobic condition explored in the previous study, and the aerobic oxidation of dihydrobezothiazole byproduct **2**, we have thus been able to obtain desired benzothiazoles in good to excellent yields.

Focusing on the key step of the mechanism, our previous study was conducted with the preformed Schiff bases.[8] Addressing the synthetic objectives we now present a simplified version of the benzothiazole forming process and use disulfide amine **4** and aldehyde **5** instead (Scheme 3). Lead-



4 **5** **1** **2**

Scheme 3. Benzothiazole formation.

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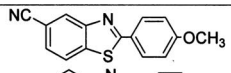
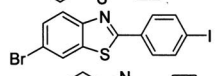
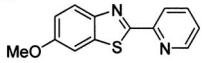
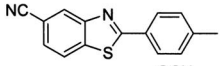
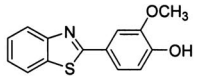
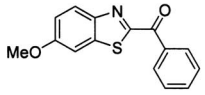
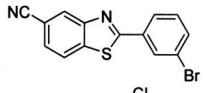
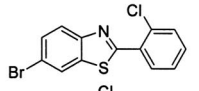
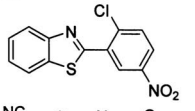
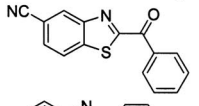
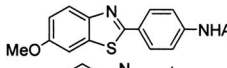
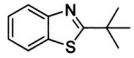
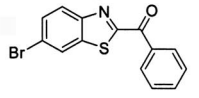
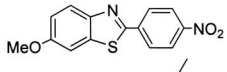
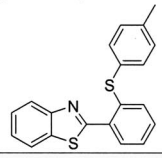
ing to virtually the same yields, the current variation has thus shown an equal, if greater synthetic efficiency compared to the previous two step process.

To demonstrate the synthetic potential and examine the synthetic scope of the method various substrates were treated under the reaction conditions. The results of the investigation are depicted in Table 1.

Table 1. Investigation of the reaction scope.

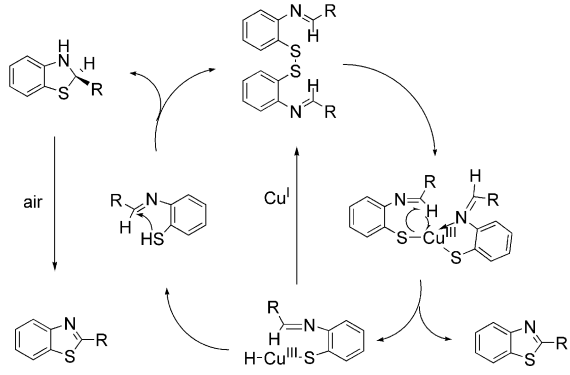
Entry	Disulfide **4** X =	Aldehyde **5** R =	Benzothiazole **2**	Yield
a	5-CN	4-methoxyphenyl		72%
b	4-Br	4-iodophenyl		82%
c	4-OMe	2-pyridyl		77%
d	5-CN	*p*-tolyl		77%
e	H	4-hydroxy-3-methoxyphenyl		70%
f	4-OMe	benzoyl		66%
g	5-CN	3-bromophenyl		74%
h	4-Br	2-chlorophenyl		88%
i	H	2-chloro-5-nitrophenyl		78%
j	5-CN	benzoyl		69%
k	4-OMe	4-(acetylamino)phenyl		80%
l	H	*tert*-butyl		77%
m	4-Br	benzoyl		85%
n	4-OMe	4-nitrophenyl		86%
o	H	2-(*p*-tolylmercapto)phenyl		76%

General procedure: The mixture of aldehyde (0.005 mol) and amine disulfide (0.0025 mol) in acetic acid (5 mL) was stirred in presence of Cu^{I} 3-methylsalicylate (5%) open to air and heated to 80 °C.

During optimalization a variety of solvents were explored (dioxane, THF, toluene, H_2O, DMA, AcOH) with some success. On the basis of the best isolated yield, however, AcOH proved superior to the others. The influence of moisture in the reaction media was also examined. While the reaction does not proceed in water itself, water content is not detrimental to the synthetic outcome of the transformation as the solvents were used "as is" without any drying.

Visibly missing from the list of substrates in Table 1 are aldehydes carrying an alpha hydrogen atom. Although a few cursory experiments were carried to fill this reactivity void, they did not lead to the desired reaction outcome for reasons extensively discussed in the literature.[9]

In analogy with the previous accounts,[7a,8] we suggest the reaction mechanism is centred around the Cu catalyzed scission of the S–S bond and the subsequent intramolecular C–H abstraction. Both, Fehling-like one electron, or two electron pathways can be involved, as the clear distinction between the two is, in the open-air system, ambiguous (see Scheme 4).



Scheme 4. Tentative mechanism of the reaction.

In a set of control experiments we also focused on the influence of the catalyst on the reaction outcome. From the variety of copper sources examined [CuI, CuCN, Cu_2O, $Cu(OAc)_2$ and Cu^{I}-3-methylsalicylate] leading to virtually the same results, Cu^{I}-3-methylsalicylate was selected as the catalyst of choice for its solubility in the reaction media. When, in the separate control experiment, the catalyst was fully omitted from the reaction mixture, no desired product was detected.

Conclusions

In conclusion we have presented here a novel synthetic route to benzothiazoles under relatively mild conditions. The method is built on copper-catalyzed activation of a disulfide accompanied by C–H bond activation of neighbouring imine functionality. The scope and the limitations of the process have been demonstrated on the various functionalized substrates with good to excellent yields.

Experimental Section

2,2′-Disulfanediyldianiline (0.50 mmol) was dissolved in acetic acid (2 mL) followed by aldehyde (1.1 mmol) and copper(I) 3-methylsalicylate (0.025 mmol). The mixture was stirred and heated at 80 °C for 5 hours open to air. After the reaction was complete, the

mixture was poured into water (75 mL) and the resulting precipitate was collected by filtration. The dry crude product was finally purified by column chromatography.

Supporting Information (see also the footnote on the first page of this article): A complete description of all of the experimental procedures as well as the characterization of all of the new compounds.

Acknowledgments

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