LETTERS

Cu(II)-Mediated C–S/N–S Bond Formation via C–H Activation: Access to Benzoisothiazolones Using Elemental Sulfur

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(5) Supporting Information

ABSTRACT: A copper-mediated C-S/N-S bond-forming reaction via C-H activation that uses elemental sulfur has been developed. The addition of TBAI was found to be crucial for the success of this transformation. The method is scalable, shows excellent functional group tolerance, and is compatible



with heterocycle substrates, providing efficient and practical access to benzoisothiazolones. The direct diversification of the benzoisothiazolone products into a variety of sulfur-containing compounds is also demonstrated.

n recent years, copper-catalyzed/mediated functionalization of C–H bonds to form C–C, C–N, and C–O bonds has attracted significant attention.^{1,2} In contrast, copper-catalyzed direct C-S bond formation has remained relatively undeveloped.^{3–8} This could be due to catalyst poisoning by sulfur species or the susceptibility of sulfur toward oxidative decomposition or oligomerization.³ So far, only a few examples of sulfenylation of unactivated arene C-H bonds have been reported.⁶⁻⁸ In 2006, Yu reported the first copper-mediated C-H thioetherification of 2-phenylpyridine substrates with PhSH and MeSSMe as the sulfur sources in moderate yields.⁶ Qing reported a coppermediated methylthiolation of arylpyridines using DMSO as the sulfur source. In 2012, the Daugulis group reported a copperpromoted sulfenylation of benzoic acid derivatives with disulfides employing a removable 8-aminoquinoline directing group (Scheme 1a).⁸ These established sulfenylation methods,

Scheme 1. Copper-Mediated C–H Activation/C–S Bond Formation



however, suffer from some limitations, including restricted substrate scope; the use of odorous sulfur sources, such as thiols and disulfides; and the formation of undesired toxic byproducts. Thus, identifying a generally useful and operationally convenient sulfur source is crucial for expanding the practical utility of this class of reactions. Elemental sulfur (S_8) is inexpensive, readily available, and nonodorous.⁹ Therefore, the use of elemental sulfur as a sulfur source in copper-catalyzed sulfenylation of

unactivated C-H bonds is an appealing transformation but has not been reported to the best of our knowledge.

Benzoisothiazolones are well-known five-membered sulfurand nitrogen-containing heterocycles that are ubiquitous in agrochemicals and pharmaceuticals. It has been shown that certain benzoisothiazolones and their derivatives possess anti-HIV and antifungal activities.¹⁰ In view of their biological and synthetic importance, a number of methods have been developed to access these compounds.¹¹ However, these procedures generally require multiple synthetic steps and/or use highly toxic and corrosive reagents. Therefore, the development of an efficient and environmentally benign protocol, by which a diverse library of benzoisothiazolones could be prepared from readily available starting materials, would be highly desirable.

Herein, we report the first example of copper-mediated C–S/ N–S bonds formation via C–H activation that uses elemental sulfur (Scheme 1b). This protocol uses readily available benzamide starting materials and provides a straightforward means of preparing a variety of benzoisothiazolones. We have also demonstrated that the corresponding benzoisothiazolones are versatile intermediates for the synthesis of aryl sulfides, aryl sulfoxides, saccharins, and other sulfur-containing organic compounds.

As part of our ongoing research in developing novel C–H functionalization reactions for the synthesis of heterocycles,¹² we became interested in the use of our newly developed bidentate directing group derived from (pyridin-2-yl)isopropylamine (PIP-amine) for such transformations.^{13–15} Therefore, we commenced our studies by attempting to couple benzamide **1** with S₈ in the presence of Cu(OAc)₂ and Ag₂CO₃ under aerobic conditions. Gratifyingly, the desired product **2** was obtained in 10% yield in DMF (Table 1, entry 1). TBAI is commonly employed as an efficient additive in C–S bond-forming



Received: September 15, 2014



^{*a*}Isolated yield on 0.2 mmol scale in 2.0 mL of solvent unless otherwise noted. PIP = (pyridin-2-yl)isopropyl. ^{*b*}0.2 equiv of $Cu(OAc)_2$ ·H₂O was used. ^{*c*}1.0 mL of CH₂Cl₂ was used.

reactions.^{3e,5d} Indeed, in the present reaction, the addition of 1 equiv of TBAI slightly improved the yield of 2 (entry 2). The desired product was obtained in 11% yield in the absence of silver salt (entry 3), while the use of Ag_2O led to modest improvement (25%, entry 4). $Cu(OAc)_2 \cdot H_2O$ proved to be the best promoter among various copper sources that were examined (entries 6-9). No desired product was observed in the absence of copper salt (entry 10). The yield improved to 59% when the reaction was conducted in CH₂Cl₂ (entry 11). After further screening the desired product 2 could be obtained in 89% yield under the following optimized conditions: 1.0 equiv of Cu(OAc)₂·H₂O, 2.5 equiv of Ag₂O, 2.0 equiv of S₈ and 1.0 equiv of TBAI in CH₂Cl₂ (0.2 M) under air at 90 °C for 18 h (entry 15). Both TBAI and Ag₂O are crucial for the efficiency of this transformation (entries 16-20). The connectivity of benzoisothiazolone 2 was confirmed by single-crystal X-ray diffraction (Figure S1, Supporting Information).

After identifying the optimized conditions, we next explored the substrate scope of this transformation. Both electron-rich and -deficient benzamides proceeded well to afford substituted benzoisothiazolones in moderate to high yields (Figure 1). Trifluoromethyl substituents in the ortho, meta, and para positions gave the desired products in high yields (3-5). Generally, substrates bearing electron-withdrawing groups (-CF₃, 5; -CO₂Me, 9; -CN, 10; and -NO₂, 11) gave higher yields than those bearing electron-donating groups (-OMe, 6; -Me, 7; and -OAc, 8). This qualitative trend suggests the electrophilic aromatic substitution (S_EAr) pathway was unlikely to be operative. It is worth noting that all halides, fluoride, chloride, bromide, and iodide, remained intact under the standard reaction conditions, affording the desired products in moderate to high yields (12-16). *m*-Alkoxy substrate partially led to the sulfenylation adjacent to oxygen (19b), possibly indicating that coordination of the alkoxy substituent stabilizes the aryl-copper intermediates.

In light of the biological importance of the heteroaryl-fused isothiazolones, we further investigated the compatibility of this



Figure 1. Benzamide substrate scope. Reaction conditions: substrate (0.2 mmol), $Cu(OAc)_2$ ·H₂O (0.2 mmol), Ag_2O (0.5 mmol), S_8 (0.4 mmol), and TBAI (0.2 mmol) in CH₂Cl₂ (1.0 mL) under air at 90 °C for 18 h. Isolated yield.

protocol with heterocyles (Figure 2). Gratifyingly, a wide range of heterocycles including pyridines, thiophenes and benzothio-



Figure 2. Scope of heteraryl benzamide. Reaction conditions: substrate (0.2 mmol), $Cu(OAc)_2$ ·H₂O (0.2 mmol), Ag_2O (0.5 mmol), S_8 (0.4 mmol), and TBAI (0.2 mmol) in CH₂Cl₂ (1.0 mL) under air at 90 °C for 18 h. Isolated yield.

phenes, were all tolerated under the reaction conditions, furnishing the heteroaryl-fused isothiazolones in good yields. Notably, 2-fluoroisonicotinamide reacted at the kinetically more acidic C–H bond (**21b**). This observation can be rationalized by invoking a concerted metalation/deprotonation (CMD) pathway. 5-Nitrothiophene-2-PIP-carboxamide gave thioether **30**, presumably due to the presence of a strong electron-withdrawing

group. Interestingly, benzothiophene-2-PIP-carboxamide predominantly gave the free thiol product **31b** in 64% yield.

To demonstrate the synthetic utility of this method, the reaction was performed on 5 mmol scale, producing benzoisothiazolone **2** in 80% yield (eq 1, 1.08 g).



The synthetic versatility of the products can be exploited through the diverse transformations shown in Figure 3, allowing



Figure 3. Versatile transformations of benzoisothiazolone **2** to various sulfur-containing compounds. Conditions: (a) MeMgBr, THF, rt, 2 h; (b) NaBH₄, EtOH, 0 °C to rt, overnight; (c) NaBH₄, EtOH, 0 °C to rt, 30 min; then BnBr, Et₃N, overnight; (d) 4-methylbenzenethiol, CH₂Cl₂, rt, 12 h; (e) H_3IO_{60} CrO₃ (cat.), CH₃CN, rt, 3 h; (f) 2,4,6-trichloro-1,3,5-triazine, 30% H_2O_2 , CH₃CN, rt, 1 h; (g) TMSCF₃, KF, DMF, 80 °C, overnight; (h) NaBH₄, EtOH, 0 °C to rt, 30 min; then *p*-MeOPhCOCl, overnight.

access to various sulfur-containing compounds. Treatment of benzoisothiazolone 2 with MeMgBr gave thioether 32 in 89% yield.¹⁶ Reduction of 2 by NaBH₄ gave thiophenol 33 in 84% yield. Oxidation of 2 with 30% H_2O_2 in the presence of 2,4,6trichloro-1,3,5-triazine selectively afforded sulfoxide 37 in 74% yield.¹⁷ Saccharin derivative **36** was obtained in 97% yield by the oxidation of 2 with $H_{5}IO_{6}$ in the presence of catalytic CrO_{3} .¹⁸ Notably, trifluoromethylthiolation product 38 was obtained in 68% yield when 2 was reacted with Ruppert's reagent and KF, providing a new route to aryl trifluoromethylthioarenes. Other sulfur-containing compounds, such as benzyl thioether 34, disulfide 35, and thioester 39 could also be produced by the transformation of benzoisothiazolone 2. Although the PIP group could not be directly cleaved from the benzoisothiazolone products, it can be easily removed from sulfur-containing benzamides, such as 34, by treatment with KOH and $CuCl_2$ in EtOH (eq 2).

To gain further insight into the reaction mechanism, additional experiments were conducted (Figure S3, Supporting Information). An intermolecular competition experiment between **5s**



and 7s revealed that electron-deficient arenes reacted with higher relative rates (Figure S3a, Supporting Information). Addition of 1 equiv of radical scavengers, such as TEMPO and 1,1diphenylethylene, did not inhibit the reaction (Figure S3b, Supporting Information). Addition of 1 equiv hydroquinone substantially reduced the yield but still did not completely suppress the reaction. These experiments suggest that the transformation does not proceed via radical intermediates. The intermolecular KIE between 1 and d_4 -1 gave a value of 2.6, indicating that C–H cleavage could potentially be the ratelimiting step (Figure S3c, Supporting Information). Although the exact role of TBAI is unclear at this point, we speculated that TBAI could play a role as a S₈ activator and increase the solubility of sulfur in dichloromethane.^{5d,19}

On the basis of these mechanistic studies and earlier precedents,^{20,21} a plausible mechanism appears to involve Cu(II)-mediated, disproportionative C–H activation followed by sulfur-atom transfer to form Cu(III) intermediate B.^{22,23} Subsequent N–S reductive elimination leads to benzoisothiazolone **2** and Cu(OAc) (Figure 4).²¹ Finally, Cu(OAc) is oxidized by Ag₂O/air to regenerate Cu(II), which would finish the catalytic cycle. A detailed mechanism remained to be elucidated.²⁴



Figure 4. Plausible reaction mechanism.

In conclusion, we have developed the first copper-mediated C-S/N-S bond-forming reaction via C-H activation that uses elemental sulfur as the sulfur source. The presence of a stoichiometric amount of TBAI is crucial for the success of this transformation. This reaction is scalable and tolerates a wide range of functional groups, providing an efficient means of accessing biologically important benzoisothiazolones. In addition, heterocyclic substrates are compatible with this protocol, which allows synthesis of a variety of unique heteroaryl-fused isothiazolones. The versatility of the benzoisothiazolone moiety renders this protocol highly attractive for both synthetic and medicinal chemistry.

ASSOCIATED CONTENT

Supporting Information

Experimental details, spectral data for all new compounds, and X-ray data for 2 (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support from the National Basic Research Program of China (2015CB856600), the NSFC (21422206, 21272206), the Fundamental Research Funds for the Central Universities (2014QNA3008), Qianjiang Project (2013R10033), and Special Fund for Agro-Scientific Research in the Public Interest of China (201403030) is gratefully acknowledged. We thank Dr. Keary M. Engle (California Institute of Technology) for helpful suggestions and comments.

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