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A Mild, Nonbasic Synthesis of Thioethers. The Copper-Catalyzed Coupling of Boronic Acids with *N*-Thio(alkyl, aryl, heteroaryl)imides

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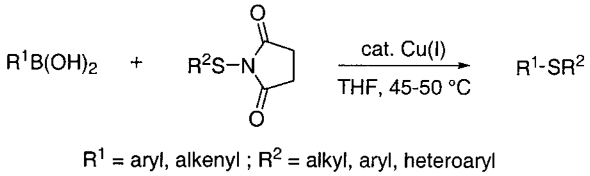
ABSTRACT

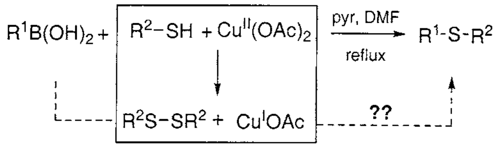


A new synthesis of thioethers is described. The reaction of boronic acids with aryl, heteroaryl, and alkyl *N*-thioimides in the presence of catalytic quantities of a Cu(I) carboxylate affords good to excellent yields of thioethers. This reaction takes place in the absence of a base under mild conditions (THF, 45–50 °C, 2.5–12 h) and represents an interesting complement to known methods for thioether synthesis.

Aryl, alkenyl, and alkyl thioethers are important intermediates in organic synthesis. In addition to their routine synthesis by the S_N2 substitution of alkylating agents with thiolate anions, a variety of other methods have been used for their preparation.[2] Even so, there still are synthetic difficulties that need to be addressed. High temperatures, several equivalents of base, or strong reducing agents are often required.[3]

A recent article by Guy and co-workers described the preparation of aryl alkyl sulfides by the reaction of arylboronic acids (2.0−2.2 equiv) and alkanethiols in the presence of stoichiometric copper $Cu(OAc)_2$ (1.5 equiv) and pyridine (3.0 equiv) in refluxing DMF (Scheme 1).[4] The authors implied a mechanism that parallels that proposed for related arylations of phenols and amines by arylboronic acids in the

Scheme 1. Copper-Mediated Coupling of Boronic Acids and Thiols



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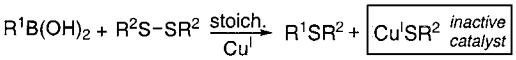
presence of Cu^{II} catalysts under oxidative conditions,[5] namely, transmetalation of the boronic acid to Cu^{II} followed by a ligand substitution to introduce the phenol or amine to the coordination sphere of the Cu. Two additional steps of undefined sequence, reductive elimination and metal oxidation, complete the process. While this mechanism likely operates for the Cu^{II}-mediated arylation of phenols and amines by arylboronic acids, it is unlikely in the case of the corresponding thiols. Why? Thiols are easily oxidized to disulfides by Cu^{II};[6] therefore, it is most probable, particularly given the harsh reaction conditions, that the transformation described by Guy and co-workers is actually a Cu^{I}-mediated coupling of an arylboronic acid with a dialkyl disulfide (both the Cu^{I} and the dialkyl disulfide can be generated in situ under Guy's reaction conditions). If so, it might be feasible to generate thioethers under much milder conditions by coupling boronic acids with disulfides or disulfide equivalents using a Cu^{I} catalyst.

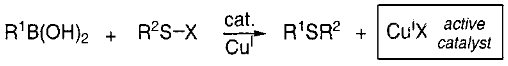
In support of this mechanistic speculation, diphenyl sulfide was formed in 74% yield when diphenyl disulfide and phenylboronic acid were treated with 1.3 equiv Cu^{I}-3-methylsalicylate (CuMeSal)[7] in DMA for 18 h at 100 °C (Scheme 2). While this experiment demonstrated the potential for *S*-arylation under nonbasic conditions, it also revealed the empirical requirement for stoichiometric Cu^{I} in the reaction. Alhough the putative mechanism is catalytic in Cu^{I}, the observed requirement for stoichiometric Cu^{I} can be understood if half of the disulfide is converted into a catalytically inactive Cu^{I}-thiolate. If true, then appropriate modification of the disulfide moiety could render this process catalytic in Cu^{I} and deliver a valuable addition to the repertoire of methods for the construction of thioethers (Scheme 3).

Scheme 2. Copper-Mediated Coupling of Boronic Acids and Disulfides



$$R^1B(OH)_2 + R^2S{-}SR^2 \xrightarrow[Cu^I]{stoich.} R^1SR^2 + \boxed{Cu^ISR^2 \text{ inactive catalyst}}$$

Scheme 3. Copper-Catalyzed Coupling of Boronic Acids and Disulfide Equivalents



$$R^1B(OH)_2 + R^2S{-}X \xrightarrow[Cu^I]{cat.} R^1SR^2 + \boxed{Cu^IX \text{ active catalyst}}$$

We now report the CuMeSal-mediated coupling of *N*-thioimide derivatives with boronic acids as a new route to thioethers. Many organoboron reagents are now readily available, and more than 350 *N*-thioimides (*S*-alkyl, -aryl, -heteroaryl, -alkenyl) have been described in the literature[8] and used as sources of electrophilic sulfur.[9] *N*-Thioimides are easily and efficiently prepared from their corresponding thiols and *N*-chlorosuccinimide,[10] or by reaction of the corresponding disulfide with 2 equiv of an *N*-bromoimide.[11] The *N*-thioimides **2−6** used in this study (Figure 1) were prepared by the first method, while *N*-thiophthalimide **1** was prepared by the reaction of dimethyl disulfide with *N*-bromophthalimide.[12] Some thioimides, such as *S*-methyl- and *S*-phenyl-*N*-thiophthalimide, are now commercially available.

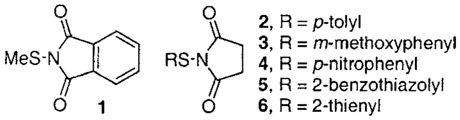


Figure 1. *N*-Thioimides used in this study.

As depicted in Table 1, treatment of a boronic acid (1.5−2.0 equiv) with an *N*-thioimide (1.0 equiv) in the presence of 20−30% CuMeSal in THF at 45−50 °C afforded thioethers in moderate to good yields (51−79%) within 2−12 h. The only exception was the unsuccessful coupling of *Z*-*β*-styrylboronic acid with *N*-thioimide **3** (entry 6), which contrasts with the successful coupling achieved using the isomeric *E*-*β*-styrylboronic acid (entry 5). In the former case, the *Z*-*β*-styrylboronic acid is essentially unchanged after 24 h under the reaction conditions. The lack of reactivity cannot be attributed to steric effects alone, since *o*-tolylboronic acid couples rapidly and in good yield with *N*-thioimide **3** (entry 7). Electron-withdrawing groups as well as electron-donating

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[4] Herradura, P. S.; Pendola, K. A.; Guy, R. K. *Org. Lett.* **2000**, *2* (14), 2019−2022.

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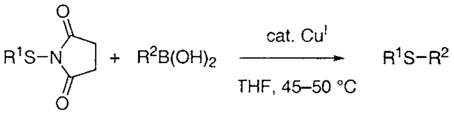
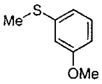
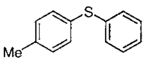
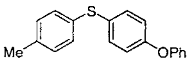
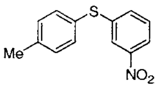
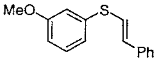
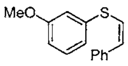
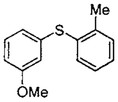
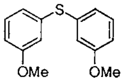
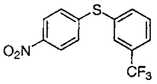
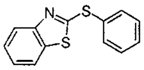
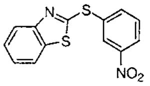
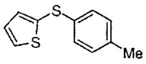
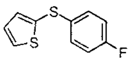
[12] Klose, J.; Reese, C. B.; Song, Q. *Tetrahedron* **1997**, *53*, 14411−14416.

Table 1. Cu^I-Catalyzed Synthesis of Thioethers



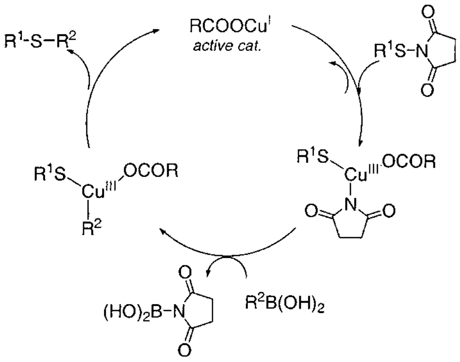
entry	*N*-thio-imide	R^2	product	%
1	**1**	3-methoxyphenyl		79
2	**2**	phenyl		60
3	**2**	4-phenoxyphenyl		70
4	**2**	3-nitrophenyl		51
5	**3**	*E*-β-styryl		72
6	**3**	*Z*-β-styryl		trace
7	**3**	*o*-tolyl		83
8	**3**	3-methoxyphenyl		71
9	**4**	3-trifluoromethylphenyl		69
10	**5**	phenyl		57
11	**5**	3-nitrophenyl		56
12	**6**	*p*-tolyl		71
13	**6**	4-fluorophenyl		76

groups on both the *N*-thioimide and boronic acid partners were compatible with the reaction conditions. Nitroaryl sulfides, which cannot be obtained with protocols involving the use of strong reducing reagents, were easily synthesized using this new reaction (entries 4, 9, and 11). Finally, heteroaromatic *N*-thioimides **5** and **6** also underwent the coupling (entries 10−13).

As a suitable control experiment, no reaction was observed after treating the *N*-thiosuccinimide derivative **2** with the phenylboronic acid at 50 °C for 24 h in THF; however, upon addition of catalytic CuMeSal the reaction commenced and was completed efficiently within 4 h. This new coupling gave best yields with 1.5−2.0 equiv of the boronic acid, although in some cases this amount could be diminished without affecting the yield. Among the various solvents tested (dimethylacetamide, THF, EtOH, dioxane, *N*-methylpyrrolidone, toluene, dichloroethane), dioxane and THF were the best. The reaction was rapid in most cases (3−4 h) at 45−50 °C. The use of bases (TBAF, K_2CO_3, NaOH, pyridine, Et_3N) inhibited the reaction. The corresponding disulfides could be used in place of the *N*-thioimide, although stoichiometric copper(I) carboxylate was required.

From a mechanistic perspective, the coupling may start with a reversible oxidative addition[13] of the *N*-thioimide to Cu(I), followed by a transmetalation from boron to copper (Scheme 4). Carbon−sulfur reductive elimination would afford the thioether and regenerate a catalytically viable Cu^I carboxylate. Consistent with this premise, different copper(I) carboxylates were effective (CuMeSal,[7] CuOAc, CuTC[14]), but no reaction was observed with CuCN, Cu_2O, or CuCl. These observations suggest that the transmetalation step in Scheme 4 delivers the imide moiety to the boron and that the catalytic cycle is carried by the copper(I) carboxylate. For clarity, we depict the coupling proceeding through a $Cu^I−Cu^{III}$ mechanism. We note, however, that the reaction of disulfides with Cu^I has been studied in detail and is dramatically sensitive to the structure of the disulfide. Whether the disulfide is cleaved and, if so, the oxidation state of the copper cannot be easily predicted.[15]

Scheme 4. Possible Mechanism of the Copper-Catalyzed Coupling of Boronic Acids and *N*-Thioimides



In conclusion, we have described a new, base-free, and mild method for the synthesis of thioethers, which provides a useful alternative to known copper-mediated routes to thioethers that proceed under basic conditions.[2p,4] The CuMeSal-catalyzed cross-coupling of organoboronic acids and *N*-thioimide derivatives afforded the desired thioethers in moderate to good yields.

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[13] Cohen, T.; Wood, J.; Dietz, A. G., Jr. *Tetrahedron Lett.* **1974**, 3555−3558.

[14] Cu^I-thiophene-2-carboxylate is commercially available from Frontier Scientific Inc. of Logan, Utah.

[15] See, for example: Itoh, S.; Nagagawa, M.; Fukuzumi, S. *J. Am. Chem. Soc.* **2001**, *123*, 4087−4088.

Acknowledgment. The National Cancer Institute, DHHS supported this investigation through grant No. CA40157. We are most grateful to Dr. Gary Allred of Frontier Scientific, Inc. of Logan, Utah for facilitating this study with a generous supply of boronic acids.

Supporting Information Available: A complete description of experimental details and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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