Organic LETTERS

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Neutral Sulfur Nucleophiles: Synthesis of Thioethers and Thioesters by Substitution Reactions of N-Heterocyclic Carbene Boryl Sulfides and Thioamides

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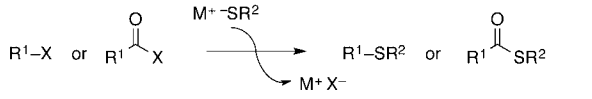
Supporting Information

ABSTRACT: Newly discovered boryl sulfides and *N*-borylthioamides are shown to serve as neutral sources of sulfur nucleophiles in substitutions reactions. For example, heating of diMe-Imd-BH(SPh)$_2$ with benzyl bromides, primary bromides, or acid chlorides provides the corresponding thioethers or thioesters in high yields. Likewise, *N*-phenyltetrazole thioethers/esters are made from a readily available *N*-borylthionotetrazole. The formation of the boryl sulfide and its onward nucleophilic substitution can be telescoped down to a one-pot reaction whose components are an NHC−borane (NHC-BH$_3$), a disulfide, and an electrophile.

Thioethers and thioesters are important functional groups in organic chemistry and biochemistry that are classically made by substitution reactions of reactive alkyl halides or sulfonates[1] with metal thiolates (M^+-SR^2 in Figure 1a).

(a) Synthesis of thioethers and thioesters by thiolate substitution



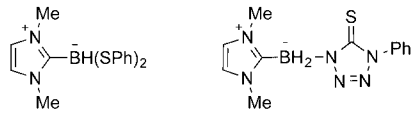
X is a leaving group, reactions occur by S_N2 pathway or with metal catalysis

(b) NHC-boranes as neutral sources of nucleophiles

1
a good hydride donor

2, n = 1,2
Y will be a nucleophile?
hydride will be a nucleophile?

(c) NHC-borylsulfide and thioamide reagents used in this study



3 **4**

Figure 1. Can NHC-boryl sulfides and thioamides serves as neutral sources of sulfur nucleophiles that replace metal thiolates?.

Thiolates are also used in modern transition metal-catalyzed substitutions,[2a] while silylthioethers are used in lanthanide-catalyzed reactions.[2b] The sulfur precursors in most of these reactions are thiols, which can be inconvenient to handle because they smell bad and because they are easily oxidized. Metal thiolates are also easy to oxidize.

We and Mayr recently reported that N-heterocyclic carbene boranes (NHC-boranes) such as 1,3-dimethylimidazolylidene borane **1**, are relatively good hydride donors, especially considering that they are neutral, not anionic.[3] Despite this property, NHC-boranes are easy to handle and are stable to air, water, and chromatography.[4] Based on the hydride character of **1**, we wondered whether NHC-boranes of the general structure NHC-BH$_{3-n}$Y$_n$ (**2**, where Y is a potential nucleophile) could be neutral sources of other kinds of nucleophiles besides hydride (Figure 1b). Here, we report that typical NHC-boryl sulfides and thioamides serve as neutral sources of sulfur nucleophiles in substitution reactions to make thioethers and thioesters.

Although unknown until recently, NHC-boryl mono- and disulfides [NHC-BH$_2$SR and NHC-BH(SR)$_2$] are readily available by direct reactions of NHC-boranes with disulfides.[5] Boryl thioamides (NHC-BH$_2$NC(=S)R) that are potential S-nucleophiles arise from similar reactions of NHC-boranes with suitable diheteroaryl disulfides. Like the parent NHC-boranes, the boryl sulfides and thioamides are stable to ambient conditions and to chromatography. In radical chemistry, they initiate polymerizations[6] and help with reductions of halides by polarity reverse catalysis.[7]

To study the substitution reactions of NHC-boryl sulfides and thioamides, we chose readily available boryl disulfide **3** and *N*-boryltetrazole thione **4** (Figure 1 c), both of which are stable white solids that are made in one step from **1** and the corresponding disulfide.[5] The disulfide **3** bears two SPh groups and represents a class of *S*-aryl boryl sulfides. The *N*-boryltetrazole thione **4** bears a B−N bond and represents a class of *N*-heteroaryl boranes with a thioamide structure embedded in a heterocycle (here a tetrazole). Substituted boranes like **4** are potential ambident nucleophiles, reacting either at sulfur or nitrogen. If S-alkylation occurs with **4**, then

Received: April 7, 2014
Published: May 6, 2014

   dx.doi.org/10.1021/ol5010164 | *Org. Lett.* 2014, 16, 2728−2731

the product *N*-phenyltetrazolyl sulfides are potential precursors for Kocienski–Julia olefinations.[8]

Table 1 shows results of some preliminary NMR experiments that were conducted to identify a suitable reaction solvent.

Table 1. Percent Conversions in a Solvent Survey in NMR Tubes

$PhCH_2Br \xrightarrow[\text{rt, solvent}]{\textbf{3} (1.1\ \text{equiv})} \underset{\textbf{5a}}{PhCH_2SPh}$

solvent	2 h (%)	4 h (%)
C_6D_6	19	30
$CDCl_3$	59	79
CD_3CN	>95	
DMSO-d_6	>95	

Spectra of mixtures of disulfide **3** (1.1 equiv) and benzyl bromide in four deuterated solvents at rt were recorded at 2 and 4 h. The ratio of phenyl benzyl sulfide **5a** to benzyl bromide is recorded as the percent conversion in Table 1. The reactions in DMSO-d_6 and CD_3CN were already complete after 2 h. The reaction in $CDCl_3$ was 79% complete after 4 h, while that in C_6D_6 was only 30% complete. Clearly. this substitution is favored by polar solvents. In addition, toluene was not detected in any of these experiments, so **3** is a source of sulfide, not hydride.

We next studied the scope of the substitutions under fixed conditions selected to accommodate **3**, **4** (1.1 equiv) and diverse benzyl bromides (1 equiv, CH_3CN, 80 °C, 3 h). Figure 2a shows the generic reaction with **3**, while Figure 2c shows the structures and isolated yields of the benzyl phenyl sulfide products **5a–g**. The reported yields are after flash chromatography. All of the benzyl bromides, regardless of substituent, provided the products in high yields (89–99%) after 3 h of heating in acetonitrile.

Next, the same suite of reactions was conducted with *N*-boryltetrazole thione **4** (1.1 equiv) under the same conditions (Figure 2b). Again, all reactions were complete in 3 h, and uniformly high isolated yields of *S*-alkylated benzylthio *N*-phenyltetrazoles **6a–6g** (88–98%, Figure 2c) were obtained after flash chromatography. Although N-boryltetrazole thione **4** might be in equilibrium with its *S*-boryl isomer (NHC-BH_2SPT) by 1,3-boryl shift under these conditions,[5] there was no evidence of formation of N-alkylation regioisomers **7a–g** in any of these reactions.

Substitution reactions were next conducted between boryl disulfide **3** and five primary bromides under the standard conditions. Not surprisingly, the reactions were slower, so the reaction time was extended to 12 h prior to solvent evaporation and flash chromatography. The product structures **8a–e** and isolated yields are shown in Figure 3.

Reaction of **3** with 6-bromo-1-hexene gave only 6-phenylthio-1-hexene **8a** in 98% yield. There was no evidence of the cyclized product, (phenylthiomethyl)cyclopentane ($PhSCH_2$–*c*-C_5H_9). Thus, the result of this radical probe experiment is negative. Reactions with three other primary bromides gave products **8b** (93% from 1-bromo-3-phenylpropane), **8c** (92% from ethyl 3-bromopropanoate), and **8d** (97% from 2-(3-bromopropyl)-isoindoline-1,3-dione).

The reaction of **3** with a propargyl bromide (1-(trimethylsilyl)-3-bromopropyne) gave **8e** in 97% yield. Finally, thioamide **4** did not react with the simple primary bromides at

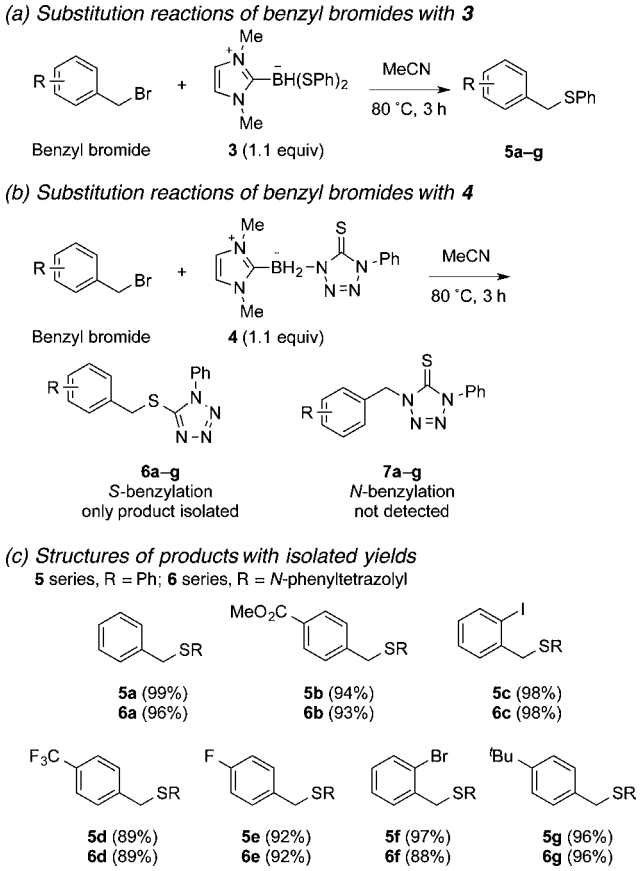


Figure 2. Scope study of substitution reactions of benzyl bromides by **3** under standard conditions

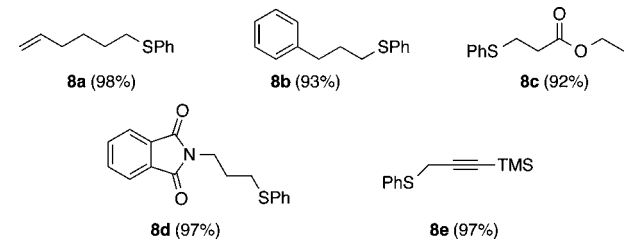


Figure 3. Structures and isolated yields of products **8** from reactions of **3** with primary bromides. Key: 0.2 M in acetonitrile at 80 °C for 12 h, then cooling, solvent evaporation, and flash chromatography.

80 °C, but it did react with the propargyl bromide to give $PTSCH_2CCTMS$ in 96% yield.

Extending the scope to make thioesters, we reacted **3** and **4** with readily available acid chlorides. Figure 4 shows the generic reaction along with the product structures and isolated yields. The reaction of benzoyl chloride with **3** was rapid (2 h) when conducted at rt in chloroform, and *S*-phenylbenzothioate **9a** was isolated by flash chromatography in 96% yield. Likewise, reactions of **3** with 2-furoyl and 2-thiophenecarbonyl chloride gave thioesters **9b** and **9c** in 94% and 97% yields, while the reaction with (4-methoxylphenyl) acetyl chloride gave **9d** in 97% yield. Finally, reaction of **3** with cinnamoyl chloride gave only the substitution product **9e** in 91% yield with no evidence of a conjugate addition product.

Longer reaction times were needed to produce good yields of thioesters from acid chlorides and the *N*-boryltetrazole thione **4**. Heating **4** with benzoyl chloride and 2-furoylcarbonyl

dx.doi.org/10.1021/ol5010164 | *Org. Lett.* 2014, 16, 2728–2731

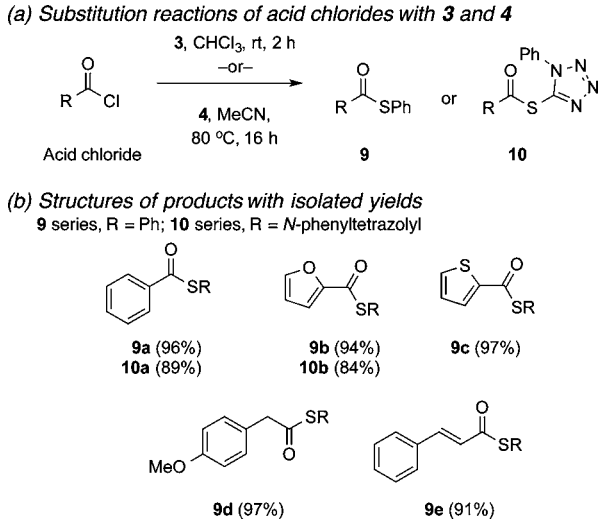


Figure 4. Synthesis of thioesters from acid chlorides.

chloride for 16 h in MeCN provided the corresponding thiol(phenyltetrazolyl) esters **10a** and **10b** in 89% and 84% yields. Again there was only S-acylation with no evidence for formation of N-acylation products.

We also conducted a series of reactions designed to telescope together the formation of the boryl sulfide reagent and the subsequent S-alkylation or S-acylation. Results for several S-alkylation reactions are summarized in Figure 5. These succeed

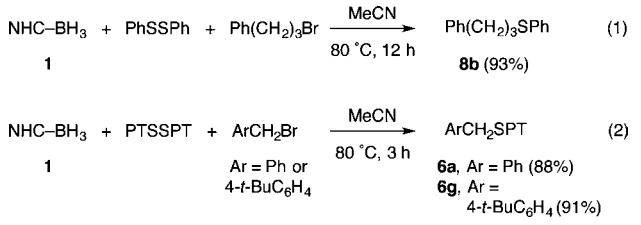


Figure 5. One-pot benzylations work in a "mix everything" mode (isolated yields after flash chromatography). NHC = 1,3-dimethylimidazolylidene; PT = *N*-phenyltetrazolyl.

when everything is simply mixed at the outset. In the reaction of Figure 5, eq 1, a mixture of parent NHC-borane **1**, diphenyl disulfide, and 1-bromo-3-phenylpropane was heated in acetonitrile under the same conditions as in Figure 3 (80 °C, 12 h). Standard evaporation and flash chromatography provided product **8b** in 93% yield.

In this reaction, we suggest that the NHC-boryl monosulfide (NHC-BH_2SPh) is first formed in situ from **1** and the disulfide.[5] In turn, this can undergo S-alkylation to form **8b** in competition with formation of disulfide **3**. If **3** is formed, it can also give S-alkylation product **8b**. This one-pot reaction gives about the same yield as the two-step reaction (**1** → **3** → **8b**), but it is more atom-efficient because only 1 equiv of diphenyl disulfide is used. Formation of **3** from **2** requires 2 equiv of the disulfide.[5]

Likewise, telescoped reactions between benzyl bromide and 4-*tert*-butylbenzyl bromide with NHC-borane **1** and *N*-phenyltetrazolyl disulfide (PTSSPT) under the usual conditions (MeCN, 80 °C, 3 h) gave products **6a** and **6g** in 88% and 91% yields (Figure 5, eq 2). Presumably, the disulfide and **1** first react to give the kinetic S-borylation product (NHC-BH_2-SPT).[5] This may react directly with the benzyl bromide to give **6** in competition with rearrangement to **4**. Reagent **4** also reacts with benzyl bromide, so either way, **6** is produced.

In contrast to these "mix everything" procedures with the benzyl bromides, the success of the telescoped reactions with acid chlorides depended on the order of addition, as shown in Figure 6, eq 1–3. Stirring of a mixture of benzoyl chloride,

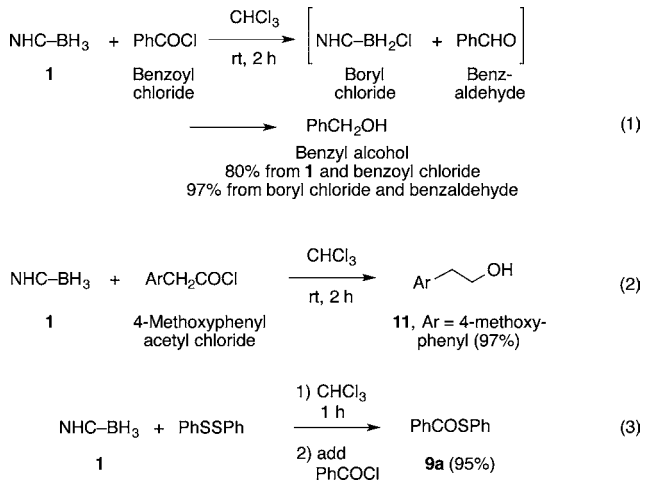


Figure 6. Results with acid chlorides depend on the order of addition: mixing everything, eqs 1 and 2, gives reduction; stepwise addition, eq 3, gives substitution.

NHC-borane **1**, and diphenyl disulfide for 2 h in $CDCl_3$ gave benzyl alcohol instead of the thioester (Figure 6, eq 1). The same result was obtained when the disulfide was omitted; benzyl alcohol was isolated in 80% yield from this experiment. So NHC-borane **1** apparently reduces acid chlorides faster than it reacts with diphenyl disulfide.

We briefly probed this reduction with two more experiments. First, (4-methoxyphenyl)acetyl chloride was reduced with 1.1 equiv of **1** in standard preparative experiment (Figure 6, eq 2). After 2 h, solvent evaporation and flask chromatography gave 2-(4-methoxyphenyl)ethanol **11** in 97% yield. This high yield shows that **1** donates two hydrides in the reduction. The presumed reductant that provides the second hydride is the NHC-boryl chloride in eq 1. To show this, the boryl chloride was generated in situ from **1** and HCl,[9] and then 1 equiv of benzaldehyde was added. After 1 h, benzyl alcohol was formed in 95% yield.

Brønsted and Lewis acids catalyze reductions of carbonyl groups by NHC-boranes.[3c,10] Unlike the parent **1**, the NHC-boryl chloride itself might act as a Lewis acid (by displacement of chloride by a Lewis base). Accordingly, we tried to reduce benzaldehyde with 1 equiv of **1** and 10 mol % of **10** (generated in situ from **1**), but only low conversion to benzyl alcohol was observed. Apparently, **10** is a stoichiometric reductant itself but not an efficient catalyst for **1**.

With an understanding of the direct reduction in hand, we then sought to prevent it during the acid chloride substitution reactions. Conveniently, this can be accomplished simply by adding the benzoyl chloride at an intermediate stage, after the boryl sulfide reagent is formed. For example, a mixture of NHC-borane **1** and diphenyl disulfide in $CHCl_3$ was stirred for 1 h, benzoyl chloride was added, and the mixture was stirred for another 1 h. Little or no benzyl alcohol was formed, and standard isolation gave thioester **9a** in 95% yield (Figure 6, eq 3).

dx.doi.org/10.1021/ol5010164 | *Org. Lett.* 2014, 16, 2728–2731

These reactions probably occur by ionic mechanisms (negative radical probe; no acceleration by light; large polar solvent effect); hence, we call them nucleophilic substitutions. Three limiting mechanisms can be considered based on timing of events: two with two steps and one concerted. In the first two-step mechanism (not shown), the boryl sulfide could dissociate to a thiolate/borenium ion pair (RS^- and $[BH_2$-NHC$]^+$), then the thiolate ion is the nucleophile that reacts with the bromide or acid chloride. This "thiolate release" mechanism seems unlikely because borenium ions are unstable.[11] Substituted NHC-boranes can express borenium-like reactivity, but far better leaving groups than thiolates are needed.[12]

The other two-step mechanism is illustrated in the upper path of Figure 7 with a monosulfide NHC-BH_2SAr and benzyl

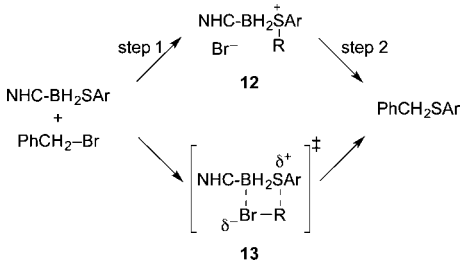


Figure 7. Possible two-step (top) and one-step (bottom) ionic mechanisms.

bromide. Here, the order of the steps is reversed. First, the sulfur of the boryl sulfide displaces the leaving group to give a transient boryl sulfonium bromide intermediate **12**. This quickly collapses by attack of bromide at boron with liberation of the thioether. (Or, the thioether can leave to form a borenium ion that is trapped by bromide.) Such nucleophilic attacks at NHC-boranes bearing good leaving groups have solid precedent.[9] Here, the neutral thioether in **12** is an outstanding leaving group for the substitution in the second step. Finally, in the concerted mechanism, Figure 7, lower path, these two processes take place simultaneously through a four-centered transition state like **13** that is polarized in a fashion similar to the intermediates in both of the two-step mechanisms.

Regardless of the mechanism, the immediate boron-containing products of these reactions are presumably boryl bromides or chlorides. To show this, several ^{11}B NMR spectra of a reaction mixture containing benzyl bromide and **3** were recorded a various intervals. The doublet from **3** gradually yielded to two new doublets assigned to NHC-BHBrSPh (−11.5 ppm, major) and NHC-$BHBr_2$ (−15.6 ppm, minor).

In summary, we have shown that NHC-boryl sulfides and related *N*-boryl thioamides are neutral reagents that deliver a nucleophilic sulfur group to provide neutral products such as thioethers and thioesters. Such neutral products are usually made from anionic sulfur nucleophiles (thiolates), while most nucleophilic substitution reactions at neutral sulfur result in cationic products (sulfonium ions, for example).

The procedures are convenient, and the synthesis of the sulfur nucleophile reagent and its onward substitution reaction are easily telescoped to a one-pot process. Only two representative S-nucleophiles were used in this work, but many related analogues are known.[5] So many kinds of thioethers and thioesters can potentially be made by using this method. Finally, the results show that hydride is not the only nucleophile that can be delivered from neutral NHC-boranes. Sulfur groups can now be delivered, so perhaps other groups will be subject to similar chemistry.

■ ASSOCIATED CONTENT

Supporting Information

Contains experimental and compound characterization details and copies of spectra of isolated products. 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

We thank the National Science Foundation for funding. We thank Dr. E. Lacôte (CNRS/University of Lyon I) for helpful discussions.

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