Integrated Synthesis of Thiényl Thioethers and Thieno[3,2-b]thiophenes via Benzo[b]thiophen-3-one

Heteroaryl thioethers are important motifs in the field of pharmaceuticals and organic materials. In particular, thiényl thioethers are potent candidates for bioactive compounds, such as endothelin inhibitors and thrombin inhibitors (Scheme 1 (i)). Several novel C-S coupling reactions have been explored to avoid the use of these harsh and toxic reaction conditions. For example, Glorius and co-workers reported Co-catalyzed dehydrogenative C-S coupling of indoles and thiols. Lei and co-workers have established electrochemical dehydrogenative C-S coupling reactions between indoles and thiols. Light-driven C-S coupling reactions have also been described. For example, the Miyake group has reported visible-light-driven C-S coupling between aryl halides and arylthiols. However, there have been a few reports on halogen- and transition metal-free C-S bond formations for the construction of thiényl thioethers. For example, Johnson and co-workers reported a p-TsOH-promoted thioether synthesis using 7-hydroxybenzo[b]thiophene. Procter and co-workers reported syntheses of thiophenes including thiényl thioethers by Ti(OH)₂-mediated C–H thiolations of arenes using methyl sulfoxides. Yorimitsu and co-workers developed acid anhydride-promoted sulfonylation reactions of aryl sulfoxides. Thus, synthetic methods for thiényl thioethers under halogen- and transition metal-free conditions are still limited, and a novel and general method to access thiényl thioethers is attractive and in demand.

To accomplish this, we focused on 3-benzo[b]thiophenone (2) which are known to be readily derived from arylthioacetic acids (1) by an intramolecular Friedel–Crafts cyclization (Scheme 1 (ii), Reaction A), and designed a novel integrated sequential approach. We expected that 2 could then be converted to 3-benzo[b]thiényl thioethers (3) via Brønsted acid-catalyzed addition of arylthiols and subsequent dehydration (Scheme 1 (ii), Reaction B). We herein report an integrated reaction system combining Reactions A and B for the synthesis of thiényl thioethers. The products were then successfully employed in Pd-catalyzed dehydrogenative cyclization reactions to prepare thienoacene derivatives (4).

Abstract A one-pot procedure for the synthesis of thiényl thioethers is described. Several thiényl thioethers were synthesized by TIOH-promoted Friedel–Crafts-type cyclization, subsequent nucleophilic attack by the arylthiol, and dehydration. This protocol was successfully applied to the synthesis of thienoacene derivatives using Pd-catalyzed dehydrogenative cyclization.

Key words Thiényl, Thiénylthioetherification, One-pot synthesis, Metal-free, Halide-free

Figure 1 Thiényl thioether skeletons in bioactive compounds and organic materials.
We first examined the thioetherification of 3-benzof[b]thiophenone (2a) with 4-methylbenzenethiol (Reaction B), that is the key step to complete our strategy, in the presence of various Brønsted acids (Table 1). The desired reaction did not occur using acetic acid, trichloroacetic acid, or trifluoroacetic acid (entries 1–3). Although thioetherification proceeded using H$_3$PO$_4$, the desired compound 3a was obtained in only 6% yield (entry 4). Further optimization revealed that sulfinic acids were suitable for thioetherification, and MsOH, TfOH, or TsOH•H$_2$O afforded 3a in 65%, 63%, and 70% yield, respectively (entries 5–7).

Since 3-benzof[b]thiophenone (2a) is relatively unstable in air and gradually decomposes, we sought to prepare the reagent in situ and developed a one-pot reaction involving Friedel–Crafts-type cyclization of 1a to afford 2a (Reaction A), followed by its thioetherification to 3a (Reaction B) (Table 2). Among the Brønsted acids examined, only TfOH was effective for both reactions A and B (Tables 1 and S5). Phenylthioacetic acid (1a) was treated with TfOH (0.0 equiv) at 40 °C for 3 h to generate 3-benzof[b]thiophenone (2a). The reaction mixture was cooled to 0 °C prior to the addition of 4-methylbenzenethiol and base (7.6 equiv), after which the mixture was heated at 80 °C for 18 h. Base was essential for formation of the desired product. Without the addition of base, the reaction B did not proceed and 3a was not obtained (entry 1), probably because the interaction between 4-methylbenzenethiol and the excess amount of TfOH would decrease the nucleophilicity of the thiol. To neutralize the excess amount of TfOH, we examined the addition of base (entries 2–6). As expected, the addition of i-Pr$_2$NEt promoted the desired reaction (entries 2 and 3). Aniline was not effective probably because its basicity was not enough (entry 4). The order of addition of the thiol and i-Pr$_2$NEt affected the yield of the desired compound 3a (Scheme S1). When i-Pr$_2$NEt was added first, 3a was obtained in only 32% yield due to the competing aldol condensation of 2a to form the dimeric compound [2,3'-bibenzof[b]thiophen]-3-ol (entry 2). When 4-methylbenzenethiol was added before i-Pr$_2$NEt, the side reaction was suppressed, and the yield of 3a increased to 64% (entry 3). We next examined several bases, and found that 2,6-lutidine gave the best result (67% NMR yield and 63% isolated yield, entry 6). Under these optimized conditions, the syntheses of several thienyl thioethers were examined (Table 3). Thioetherification with phenylthioli gave thioether 3b in 54% yield, while 2-methylbenzenethiol and 3-methylbenzenethiol gave the corresponding thioethers 3c and 3d in moderate yields. Next, several p-substituted benzenethiols were used in the reaction (3e–3j). p-Halogenated phenylthiols such as 4-chlorobenzenethiol and 4-bromobenzenethiol gave the halogenated thioethers 3e and 3f in 40% and 43% yield, respectively. Using 4-nitrobenzenethiol, the yield of the corresponding thioether 3g was notably low (21% yield) due to...
its low nucleophilicity. Benzenethiol bearing a p-acetyl amino group generated aryl thioether 3h was obtained in 45% yield. Benzenethiols containing electron-donating groups were also effective reactants. Benzenethiols bearing diphenylamino or methoxy groups at the p-position resulted in the corresponding biaryl thioethers 3i and 3j in 52% and 76% yields, respectively. Thioetherification was successful using naphthalene-1-thiol (3k, 22% yield). In contrast, naphthalene-2-thiol failed to yield the desired compound. While the reason has not been clear yet, nucleophilic attack of naphthalene-2-thiol did not proceed. Heteroaryl thiols were also applicable to the reaction. Thioetherifications using 2- or 3-thiophenethiols gave the corresponding dithiophenyl thioethers 3m and 3n in 31% and 53% yield, respectively. One of the advantages of this reaction is that it is easy to introduce a substituent on the benzothiophene skeleton because substituted precursors are readily available. Several substituted thienyl thioethers 3o–s were obtained from their respective substituted precursors 1. Beneficially, this protocol enables the easy access to highly π-expanded thioethers, such as 3t.

**Table 3** One-pot Synthesis of Several Thienyl Thioethers 3*<sup>a</sup>

<table>
<thead>
<tr>
<th>Reaction A</th>
<th>Reaction B</th>
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<tr>
<td>1 (0.20 mmol), TIOH (7.7 equiv), DCE (0.66 M), 40 °C, 3 h.</td>
<td>Reaction B: 2,6-lutidine (7.4 equiv) was added at 0 °C and heated at 80 °C, 18 h. Yields are isolated yields based on 1.</td>
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<tr>
<td>1</td>
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* Reaction A: 1 (0.20 mmol), TIOH (7.7 equiv), DCE (0.66 M), 40 °C, 3 h. Reaction B: aryliodide (1.0 equiv) and 2,6-lutidine (7.4 equiv) was added at 0 °C and heated at 80 °C, 18 h. Yields are isolated yields based on 1.
* Performed using 7.6 equiv of 2,6-lutidine.
* Performed using 1.2 equiv of thiol.
* 2,6-Lutidine was added, prior to thiol at −78 °C.
* 2,6-Lutidine was added, prior to 0 °C.
* 0.4 mmol scale.

To clarify the mechanism of reaction B, density functional theory (DFT) calculations were performed. Based on these calculations, a plausible mechanism is proposed (Scheme 2).<sup>14</sup> First, the carbonyl group of 3-benzothiophene is protonated by TIOH, while a second oxygen atom of TIOH coordinates the proton of benzenethiol to form complex IM1. Next, the benzenethiol sulfur atom attacks the carbonyl group to afford IM2 via an 8-membered cyclic concerted transition state TS1.<sup>15</sup> TIOH-assisted dehydration of IM3 proceeds via an 8-membered cyclic transition state TS2 to afford the cationic intermediate IM4. Finally, IM4 is deprotonated to form the desired thienylthioether via transition state TS3. The calculated activation energy ($E_a$) of TS2 ($E_a = 15.7 \text{ kcal mol}^{-1}$) is higher than those of TS1 ($E_a = 10.5 \text{ kcal mol}^{-1}$) and TS3 ($E_a = 4.1 \text{ kcal mol}^{-1}$), suggesting that the C–O bond cleavage is the rate-determining step of this reaction.

**Scheme 2** A Plausible Mechanism for Reaction B. Gibbs Free Energies in kcal mol$^{-1}$ are Shown in Parentheses

We next focused on a transformation of thienyl thioethers to BTBT derivatives by Pd-catalyzed dehydrogenative cyclization. Pd-catalyzed dehydrogenative coupling reactions has been established as a powerful method for the formation of heteroaromatics.<sup>16</sup> However, to the best of our knowledge, this method has not been used for the efficient dehydrogenative construction of thiophene rings. Compound 3o was used as a model to examine Pd-catalyzed dehydrogenative coupling (Table 4). In the presence of Pd(OPiv): (10 mol %) and AgOPiv (3.0 equiv), 3o was heated at 170 °C for 24 h. We found that the addition of 2,6-lutidine was essential for the reaction. Without 2,6-lutidine, the desired compound 4o was obtained in only 35% yield (entry 1).<sup>17</sup> The yield of 4o increased with the quantity of 2,6-lutidine used; using 1.0 equiv of 2,6-lutidine resulted in 54% yield (entry 2) which increased to 88% with 5.0 equiv (entry 4). While the role of 2,6-lutidine is not yet clear, it would be expected to interact with the Pd catalyst and suppress C–S bond fission.
Under the optimized conditions, the syntheses of several BTBT derivatives were examined (Table 5). BTBT (4b) and substituted BTBTs (4a and 4e) were readily obtained. The advantages of this method are (i) a ready introduction of substituents and (ii) an easy alternation of the benzene ring to other heterocycles, such as thiophene (4m).

Finally, we examined the telescoping synthesis of 4o from 4-methylbenzenethiol (5) (Scheme 3). A solution of 5 in 3 M NaOH aq. was treated with chloroacetic acid to afford 1b. The reaction was quenched with HCl aq. and extracted with CHCl₃. After removal of the solvent, the crude product was used in the one-pot procedure without further purification to afford a crude solution of 3o, which was quenched with sat NaHCO₃ aq. and extracted with CHCl₃. Following removal of the solvent, the crude mixture was used in the Pd-catalyzed dehydrogenative reaction to afford the desired BTBT derivative 4o in an overall 46% yield.¹⁸ This result suggests that our protocol can be used to prepare a variety of thieryl thioethers and BTBT derivatives from easily accessible chloroacetic acid and the appropriate arylthiol.

In conclusion, we developed a transition metal- and halide-free one-pot synthesis of thieryl thioethers. Several novel thioethers were readily synthesized using the optimized conditions. An efficient conversion of the thioethers to thienothiophenes was also established. We also demonstrated a telescoping synthesis of a thienothiophene from an arylthiol. This strategy enables the efficient and easy synthesis of 3-benzothiophene thioethers and thienothiophenes. Further applications of this strategy are currently being investigated in our laboratory.

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Click here to insert acknowledgment text. Funding sources and grant numbers should be given above in the Funding Information section.

### Supporting Information
YES (this text will be updated with links prior to publication)

### Primary Data
NO (this text will be deleted prior to publication)

### References and Notes


(9) For the structure of 3a. See a colorless liquid (32.3 mg, 0.13 mmol, 63%). 1H NMR (400 MHz, CDCl3) δ 2.28 (s, 3H), 7.03 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H). 2.75–7.40 (m, 2H). 7.62 (s, 1H). 7.78–7.83 (m, 1H). 7.86–7.90 (m, 1H). 13C NMR (100 MHz, CDCl3) δ 20.9, 122.9, 123.0, 124.7, 124.9, 125.4, 130.1, 132.6, 134.2, 136.9, 139.0, 140.0. For the detail of the calculations, see the Supporting Information.

(10) For further details of the base optimizations, see Table S6.