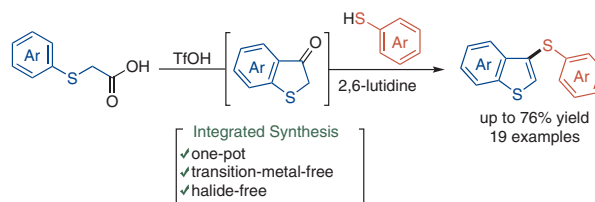


Integrated Synthesis of Thienyl Thioethers and Thieno[3,2-*b*]thiophenes via 1-Benzothiophen-3(2*H*)-ones

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

Key words thienyl thioethers, thioetherification, one-pot synthesis, metal-free, halide-free, thienoacenes

Hetaryl thioethers are important motifs in the fields of pharmaceuticals¹ and organic materials.² In particular, thienyl thioethers are potent candidates for bioactive compounds such as endothelin inhibitors^{3a} and thrombin inhibitors^{3b} (Figure 1). Hetaryl thioether moieties are also found in π -expanded thienoacene derivatives, such as [1]benzothieno[3,2-*b*][1]benzothiophene (**BTBT**), which are used as core units in high-performance semiconductors (Figure 1).⁴

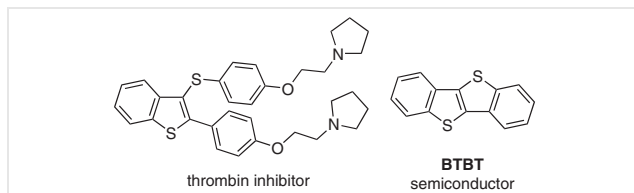
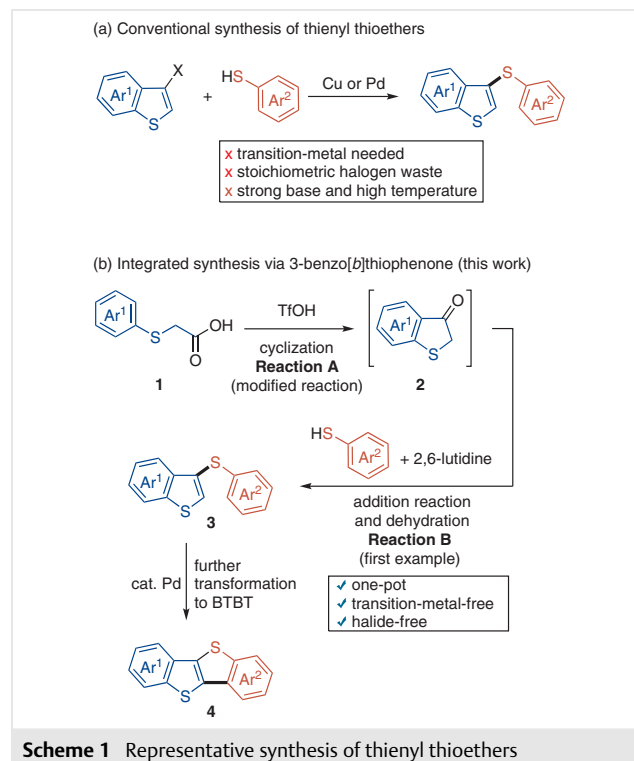


Figure 1 Thienyl thioether skeletons in a bioactive compound and an organic material

Conventional syntheses of thioethers involve transition-metal-catalyzed cross-coupling reactions between haloarenes and thiophenols, typically requiring the use of strong bases and high temperatures (Scheme 1a).⁵ Several

novel C–S coupling reactions have been explored to avoid the use of these harsh and toxic reaction conditions.^{6–8} For example, Glorius and co-workers reported a Co-catalyzed dehydrogenative C–S coupling of indoles and thiols.^{6a} Lei and co-workers established an electrochemical dehydrogenative C–S coupling reaction between indoles and thiols.^{7a} Light-driven C–S coupling reactions have also been described;⁸ for example, the Miyake group reported a visible-light-driven C–S coupling between aryl halides and arylthiols.^{8a}



There have also been a few reports on halogen- and transition-metal-free C–S bond-formation reactions for the construction of thienyl thioethers.⁹ For example, Johnson and co-workers reported a TsOH-promoted thioether synthesis from 7-bromo-3-hydroxybenzo[*b*]thiophenes.^{9a} Procter and co-workers reported syntheses of thioethers, including thienyl thioethers, by Tf₂O-mediated C–H thiolations of arenes by methyl sulfoxides.^{9b} Yorimitsu and co-workers developed acid-anhydride-promoted sulfanylation reactions of aryl sulfoxides.^{9c} However, methods for synthesizing thienyl thioethers under halogen- and transition-metal-free conditions remain limited, and a novel and general method to access thienyl thioethers is attractive and in demand.

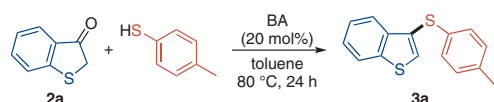
To accomplish this, we focused on 1-benzothiophen-3(2*H*)-ones **2**, which are known to be readily available from arylthioacetic acids **1** through intramolecular Friedel–Crafts cyclization (Scheme 1b, Reaction A),¹⁰ and we designed a novel integrated sequential approach.¹¹ We expected that **2** could then be converted into 1-benzothien-3-yl thioethers **3** through Brønsted acid catalyzed addition of arylthiols and subsequent dehydration (Scheme 1b, Reaction B). Here, we report an integrated reaction system that combines Reactions A and B for the synthesis of thienyl thioethers. The products were successfully employed in Pd-catalyzed dehydrogenative cyclization reactions to give thienoacene derivatives **4**.

We first examined the thioetherification of 1-benzothiophen-3(2*H*)-one (**2a**) with 4-methylbenzenethiol (Reaction B) in the presence of various Brønsted acids, a key step to complete our strategy (Table 1). The desired reaction did not occur when acetic acid, trichloroacetic acid, or tri-

fluoroacetic acid was used (Table 1, entries 1–3). Although thioetherification proceeded with H₃PO₄, the desired compound **3a** was obtained in only 6% yield (entry 4). Further optimization revealed that sulfonic acids were suitable for thioetherification and that MsOH, TfOH, and TsOH·H₂O afforded **3a** in yields of 65, 63, and 70%, respectively (entries 5–7).

Because 1-benzothiophen-3(2*H*)-one (**2a**) is relatively unstable in air and gradually decomposes, we sought to prepare the reactant in situ, and we developed a one-pot reaction involving a Friedel–Crafts-type cyclization of **1a** to afford **2a** (Reaction A), followed by its thioetherification to give thioether **3a** (Reaction B) (Table 2). Among the Brønsted acids examined, only TfOH was effective for both Reaction A and Reaction B [Table 1 and Supporting Information (SI), Table S1]. Phenylthioacetic acid (**1a**) was treated with TfOH (8.0 equiv) at 40 °C for three hours to give 1-benzothiophen-3(2*H*)-one (**2a**). The reaction mixture was then cooled to 0 °C, 4-methylbenzenethiol and a base (7.6 equiv) were added, and the mixture was heated at 80 °C for 18 h. A base was essential for the formation of the desired product. Without the addition of a base, Reaction B did not proceed, and **3a** was not obtained (Table 2, entry 1), probably because the interaction of 4-methylbenzenethiol and the excess TfOH decreased the nucleophilicity of the thiol. To neutralize excess TfOH, we examined the addition of various bases (entries 2–6).¹² As expected, the addition of DIPEA promoted the desired reaction (entries 2 and 3). Aniline was not effective, probably because it was insufficiently basic (entry 4). The order of addition of the thiol and DIPEA

Table 1 Optimization of Reaction B: Thioetherification of 1-Benzothiophen-3(2*H*)-one (**2a**) with Various Brønsted Acids^a



Entry	Brønsted acid	Conversion ^b (%)	Yield ^b (%) of 3a
1	AcOH	9	ND ^c
2	CCl ₃ CO ₂ H	19	ND
3	CF ₃ CO ₂ H	9	ND
4	H ₃ PO ₄	17	6
5	MsOH	>95	65
6	TfOH	>95	63
7	TsOH·H ₂ O	>95	70 (63) ^d

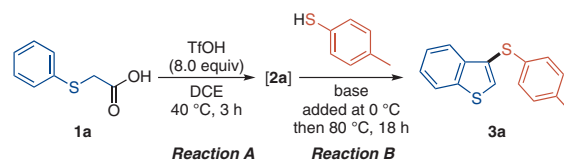
^a Reaction conditions: **1a** (0.20 mmol), Brønsted acid (20 mol%), toluene (0.2 M), 80 °C, 24 h.

^b Determined by ¹H NMR with 1,1,2,2-tetrachloroethane as an internal standard.

^c ND = Not detected.

^d Isolated yield.

Table 2 One-Pot Synthesis of Thioether **3a** via 1-Benzothiophen-3(2*H*)-one (**2a**) with Various Bases^a



Entry	Base	Yield ^b (%) of 3a
1	none	ND ^c
2 ^d	<i>i</i> -Pr ₂ NET	32
3	<i>i</i> -Pr ₂ NET	64
4	aniline	32
5	piperidine	65
6 ^e	2,6-lutidine	67 (63) ^f

^a Reaction conditions: Reaction A: **1a** (0.20 mmol), TfOH (8.0 equiv), DCE (0.66 M), 40 °C, 3 h. Reaction B: 4-methylbenzenethiol (1.0 equiv) and base (7.6 equiv) added at 0 °C, then 80 °C, 18 h.

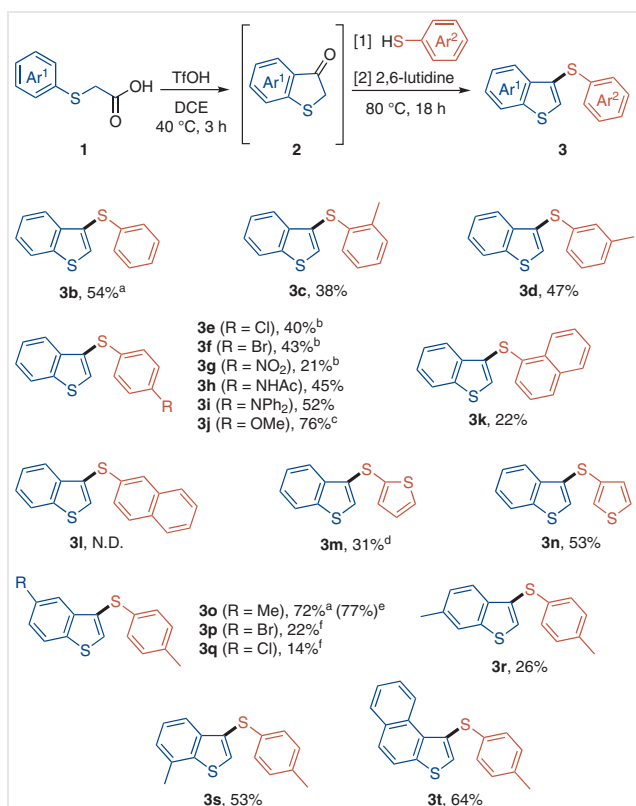
^b Yield from **1a**, determined by ¹H NMR.

^c ND = not detected.

^d Reaction B; base added before 4-methylbenzenethiol.

^e Performed with TfOH (7.7 equiv).

^f Isolated yield.



Scheme 2 One-pot syntheses of thienyl thioethers **3**. *Reagents and conditions:* Reaction A: **1** (0.20 mmol), TfOH (7.7 equiv), DCE (0.66 M), 40 °C, 3 h. Reaction B: arylthiol (1.0 equiv), 2,6-lutidine (7.4 equiv) added at 0 °C, then at 80 °C, 18 h. Yields are isolated yields based on **1**. ^a Thiol (1.2 equiv). ^b 2,6-lutidine (7.6 equiv). ^c 2,6-Lutidine was added before the thiol at -78 °C. ^d 2,6-Lutidine was added before the thiol at 0 °C. ^e 1.5 mmol scale. ^f 0.4 mmol scale.

affected the yield of the desired compound **3a** (SI; Scheme S1). When DIPEA was added first, **3a** was obtained in only 32% yield, due to the competing aldol condensation of **2a** to form the dimer 2,3'-bi-1-benzothiophene-3-ol (entry 2). When 4-methylbenzenethiol was added before DIPEA, the side reaction was suppressed, and the yield of **3a** increased to 64% (entry 3). We next examined several bases, and we found that 2,6-lutidine gave the best result (67% NMR yield and 63% isolated yield; entry 6).¹³

By using the optimized conditions, a series of thienyl thioethers were synthesized (Scheme 2). Thioetherification with phenylthiol gave thioether **3b** in 54% yield, whereas 2- and 3-methylbenzenethiol gave the corresponding thioethers **3c** and **3d** in moderate yields. Next, several *p*-substituted benzenethiols were used in the reaction (**3e–j**). 4-Chlorobenzenethiol and 4-bromobenzenethiol gave the halogenated thioethers **3e** and **3f** in yields of 40 and 43%, respectively. However, 4-nitrobenzenethiol, gave a low yield of thioether **3g** (21%), due to its low nucleophilicity. *N*-(4-Sulfanylphenyl)acetamide gave aryl thioether **3h** in 45% yield. Benzenethiols containing electron-donating groups

were also effective reactants: 4-(diphenylamino)- and 4-methoxybenzenethiol gave the corresponding biaryl thioethers **3i** and **3j** in yields of 52 and 76%, respectively. Thioetherification also proceeded successfully with naphthalene-1-thiol (**3k**; 22% yield). In contrast, however, naphthalene-2-thiol failed to yield the desired compound; although the reason is unclear, nucleophilic attack by naphthalene-2-thiol did not proceed. Hetaryl thiols also reacted successfully. Thioetherification with thiophene-2-thiol and thiophene-3-thiol gave the corresponding dithienyl thioethers **3m** and **3n** in yields of 31 and 53%, respectively. One advantage of this reaction is that it is easy to introduce a substituent onto the benzothiophene skeleton because substituted precursors are readily available. Several substituted thienyl thioethers **3o–s** were obtained from the corresponding substituted precursors **1**. Beneficially, this protocol provides easy access to highly π -expanded thioethers, such as **3t**.

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

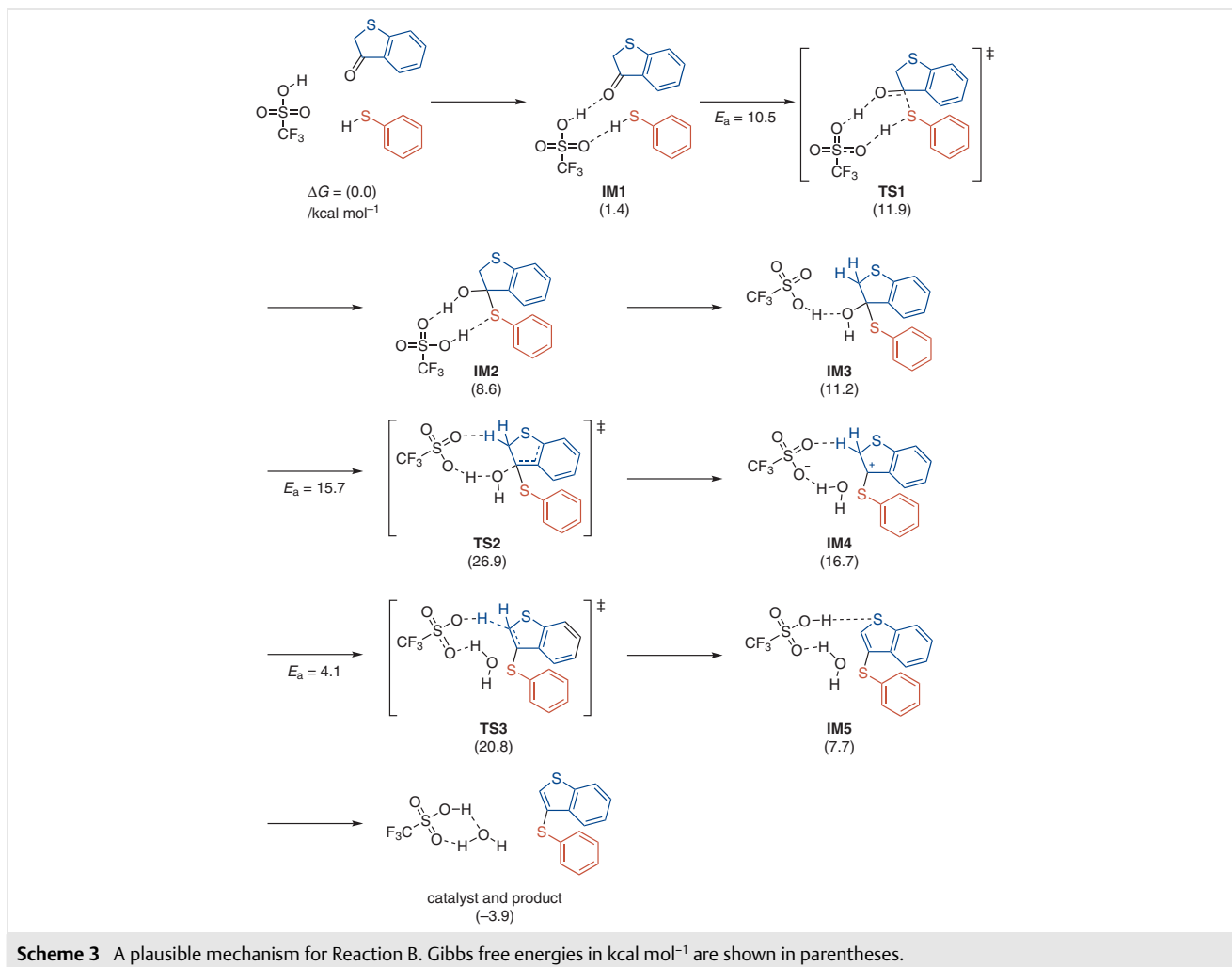
Table 3 Effect of 2,6-Lutidine on the Pd-Catalyzed Dehydrogenative Cyclization of **3o**^a

Entry	2,6-Lutidine (equiv)	Recovery ^b (%) of 3o	Yield ^b (%) of 4o
1	0	trace	35
2	1.0	ND ^c	54
3	3.0	ND	72
4	5.0	ND	88

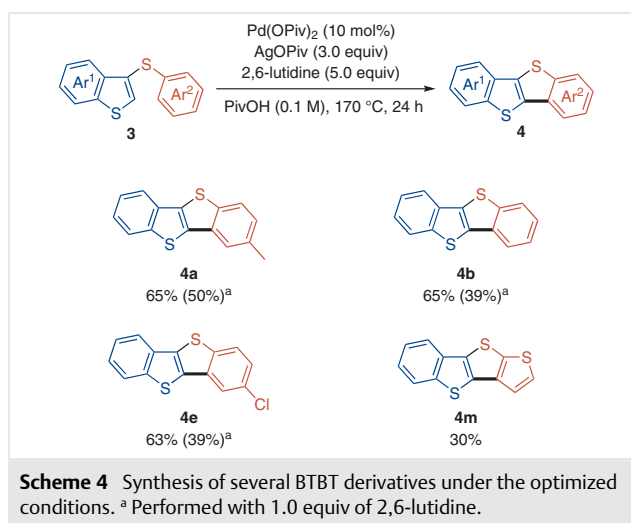
^a Reaction conditions: **3o** (0.15 mmol), Pd(OPiv)₂ (10 mol %), AgOPiv (3.0 equiv), 2,6-lutidine (0–5.0 equiv), PivOH (0.1 M), 170 °C, 24 h.

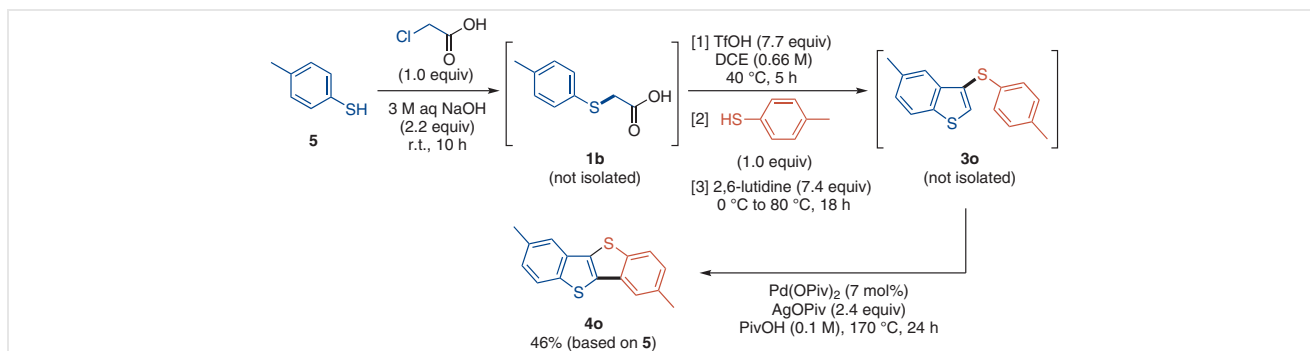
^b Isolated yield.

^c ND = not detected.



We next focused on the transformation of thienyl thioethers into BTBT derivatives by Pd-catalyzed dehydrogenative cyclization. Pd-catalyzed dehydrogenative coupling has been established as a powerful method for the formation of heteroacenes.¹⁶ 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 3). Benzothiophene **3o** was heated at 170 °C for 24 hours in the presence of Pd(OPiv)₂ (10 mol%) and AgOPiv (3.0 equiv). We found that the addition of 2,6-lutidine was essential for the reaction. In the absence of 2,6-lutidine, the desired compound **4o** was obtained in only 35% yield (Table 3, entry 1).¹⁷ The yield of **4o** increased as the amount of 2,6-lutidine increased. With 1.0 equivalents of 2,6-lutidine, the yield of **4o** was 54% yield (entry 2); this increased to 88% with 5.0 equivalents of 2,6-lutidine (entry 4). Although the role of 2,6-lutidine is not yet clear, it is likely to interact with the Pd catalyst and suppress C–S bond fission.





Scheme 5 Telescoped synthesis of **4o** from 4-methylbenzenethiol (**5**)

By using the optimized conditions, several BTBT derivatives were synthesized (Scheme 4). 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) easy replacement of the benzene ring by heterocycles such as thiophene (**4m**).

Finally, we examined a telescoped synthesis of **4o** from 4-methylbenzenethiol (**5**) (Scheme 5). A solution of **5** in 3 M aqueous NaOH was treated with chloroacetic acid to afford **1b**. The reaction was quenched with aqueous HCl and extracted with CHCl_3 . 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 saturated aqueous NaHCO_3 and extracted with CHCl_3 . After removal of the solvent, the crude mixture was used in the Pd-catalyzed dehydrogenative reaction to afford the desired BTBT derivative **4o** in an 46% overall yield.¹⁸ This result suggests that our protocol can be used to prepare a variety of thienyl thioethers and BTBT derivatives from easily accessible chloroacetic acid and the appropriate arylthiol.

In conclusion, we have developed a transition-metal-free and halide-free one-pot synthesis of thienyl thioethers. Several novel thioethers were readily synthesized by using the optimized conditions. An efficient conversion of the thioethers into thienothiophenes was also established. We also demonstrated a telescoped synthesis of a thienothiophene from an arylthiol. This strategy permits the efficient and easy synthesis of 3-benzo[*b*]thienyl thioethers and thienothiophenes. Further applications of this strategy are currently being investigated in our laboratory.

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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0040-1707280>.

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- (12) Further details of the base optimizations, see SI, Table S6.
- (13) **3-(4-Tolylsulfanyl)-1-benzothiophene (3a): One-Pot Synthesis; Typical Procedure**
TfOH (0.136 mL, 231 mg, 1.54 mmol) was added dropwise to a solution of (phenylsulfanyl)acetic acid (**1a**; 33.6 mg, 0.20 mmol) in anhyd DCE (0.3 mL), and the resulting mixture was stirred at 40 °C for 3 h then cooled to 0 °C. 4-Methylbenzenethiol (24.8 mg, 0.20 mmol) and 2,6-lutidine (0.18 mL, 1.5 mmol) were added, and the mixture was stirred at 80 °C for 18 h then cooled to r.t. The reaction was quenched with sat. aq NaHCO₃ (3 mL), and the mixture was extracted with CHCl₃ (3 × 5 mL). The combined organic phase was dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane) to give a colorless liquid; yield: 32.3 mg (0.13 mmol, 63%).
IR (neat): 3096, 3021, 1595, 1254, 1016 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 2.28 (s, 3 H), 7.03 (d, J = 8.4 Hz, 2 H), 7.11 (d, J = 8.4 Hz, 2 H), 7.35–7.40 (m, 2 H), 7.62 (s, 1 H), 7.78–7.83 (m, 1 H), 7.86–7.90 (m, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ = 20.9, 122.9, 123.0, 124.7, 124.9, 125.0, 128.4, 129.8, 130.8, 132.5, 136.0, 138.8, 140.0.
- (14) For details of the calculations, see SI.
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- (17) The structure of **4o** was confirmed by X-ray crystal structure analysis. CCDC 1961314 contains the supplementary crystallographic data for compound **4o**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.
- (18) For details, see SI.