

S-Heterocycles

Redox-Divergent Construction of (Dihydro)thiophenes with DMSO

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Abstract: Thiophene-based rings are one of the most widely used building blocks for the synthesis of sulfur-containing molecules. Inspired by the redox diversity of these features in nature, we demonstrate herein a redox-divergent construction of dihydrothiophenes, thiophenes, and bromothiophenes from the respective readily available allylic alcohols, dimethyl sulfoxide (DMSO), and HBr. The redox-divergent selectivity could be manipulated mainly by controlling the dosage of DMSO and HBr. Mechanistic studies suggest that DMSO simultaneously acts as an oxidant and a sulfur donor. The synthetic potentials of the products as platform molecules were also demonstrated by various derivatizations, including the preparation of bioactive and functional molecules.

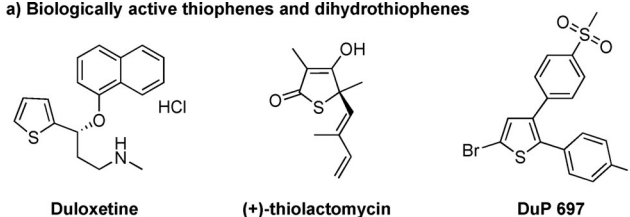
Introduction

(Dihydro)thiophenes are one of the most common five-membered heterocycles that are widespread in a large number of natural products, functional materials, and biologically active compounds.^[1] For example, duloxetine is a commercial drug that possesses effective antihypertensive activity. Thiolactomycin is a well-known thiolactone antibiotic that exhibits potent inhibitory activity against dissociable FAS enzymes.^[2] DuP 697 is an effective inhibitor of cyclooxygenase-2 (COX-2) and has anti-inflammatory, anticancer, and antipyretic effects (Scheme 1 a).^[3] Furthermore, its regioisomers show a similar COX-2 inhibitory profile.^[4] In addition, they can also serve as valuable and useful building blocks for the assembly of molecular complexity. Therefore, the construction of thiophene skeletons has attracted much attention over the last decades.^[5] Traditionally, sulfide sources such as P_4S_{10} ,^[6] K_2S/Na_2S ,^[7] H_2S ,^[8] and S_8 ^[9] were usually employed to prepare thiophene compounds through the formation of two new C-S bonds (Scheme 1 b). However, the substrates employed in these examples were highly functionalized precursors which resulted in limited scope and functional group compatibility. Moreover, although some classic methods have

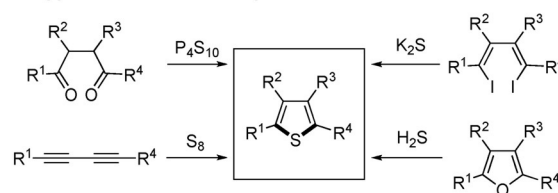
been developed to prepare substituted thiophenes, the synthesis of dihydrothiophenes is still relatively rare.^[10] In nature, important bioactive metabolites with different redox states are created by various redox enzymes. Given this in mind, we wonder if it is possible to develop a strategy of redox-divergent construction of substituted (dihydro)thiophenes from readily available starting materials under concise and metal-free conditions.

DMSO is environmentally friendly aprotic polar solvent, which has been widely used as an oxidant for alcohols,^[11] alkyl halides,^[12] epoxides,^[13] alkenes,^[14] and alkynes.^[15] Meanwhile, DMSO could also be employed as source of methyl,^[16] methine,^[17] methylene,^[18] methylthio,^[19] methylsulfinyl,^[20] and oxygen.^[21] However, there were rare reports that DMSO could be employed as sulfur donor in organic reactions.^[22] Herein, we developed a redox-divergent construction of (dihydro)thiophenes with DMSO as both an oxidant and a sulfur donor. By simply controlling the dosage of HBr and DMSO, allylic alcohols were transformed into valuable

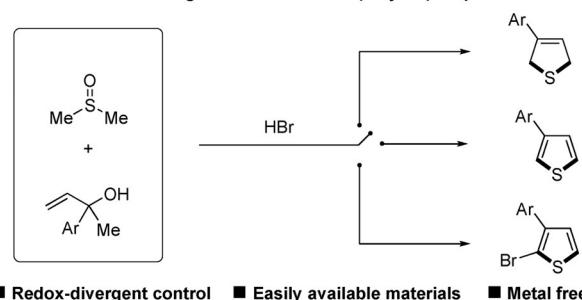
a) Biologically active thiophenes and dihydrothiophenes



b) Classic approaches to access thiophenes



c) This work: Redox-divergent construction of (dihydro)thiophenes with DMSO



■ Redox-divergent control ■ Easily available materials ■ Metal free

Scheme 1. Thiophenes and their synthesis.

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thiophenes and dihydrothiophenes in high selectivity and efficiency. Furthermore, through the further transformation of thiophene and dihydrothiophene products, various five-membered sulfur-containing heterocycles could be readily accessed.

Results and Discussion

During our initial efforts for the preparation of 2-substituted diene with allyl alcohol **1a** as the diene precursor,^[23] a small amount of thiophene **2a** and dihydrothiophene **4a** were serendipitously obtained in the presence of 2.2 equivalent of DMSO and HBr (Table 1, entry 1). Considering the important applications of such skeletons in material and medicinal chemistry, further evaluation for the formation of **2a** and **4a** was performed. An investigation of solvent revealed that **2a** could be delivered in 56% yield with exquisite selectivity in nitromethane (entries 1–4). Notably, the reaction did not work when DMSO was used as the solvent (entry 3). It probably resulted from that the excess DMSO strongly inhibited the reactivity of bromine ion generated from DMSO/HBr.^[24] The reactivity for thiophene product was further enhanced by raising the reaction temperature to 120 °C (entry 5). Whereas a higher temperature suppressed the reaction (See SI for more optimizations). It was worthy to note that 63% yield of **2a** was obtained when 33 wt% HBr solution in acetic acid was used (entry 6). The concentration examination suggested that 0.1 M was optimal for this process (entries 6–8). Other source of hydrogen bromide, such as triethylamine hydrobromide and pyridine hydrobromide, all failed to produce the desired product

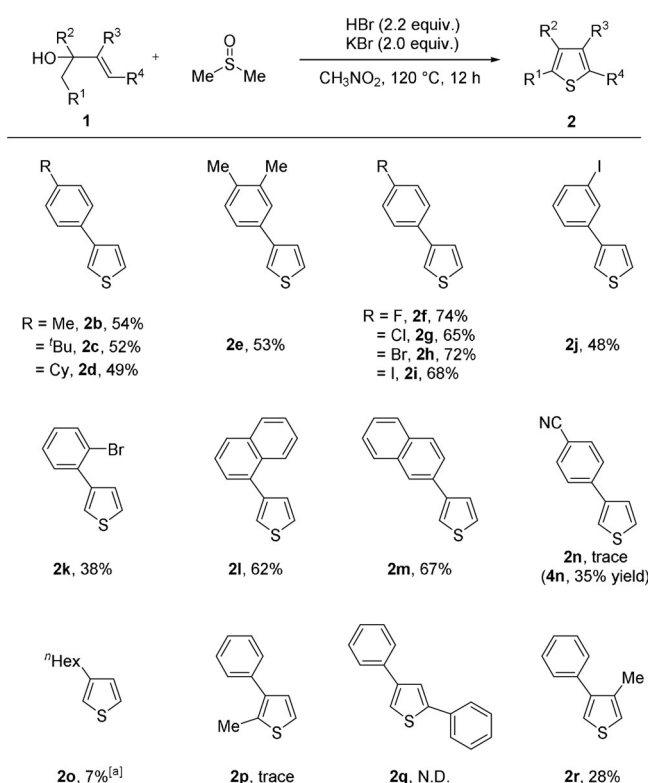
(entries 9, 10). Inspired by Chen's report,^[25] KBr was added to avoid Kornblum oxidation and the yield of **2a** was successfully improved to 72% (entry 11). Interestingly, **3a** could be obtained in 63% yield by adding another portion of hydrogen bromide (1.1 equiv) and DMSO (1.1 equiv) after 12-hours' reaction (entry 12). To our surprise, the decrease of the loading of HBr and DMSO could switch the product selectivity from thiophene **2a** to dihydrothiophene **4a**, which is difficult to be obtained via conventional methods (entry 13).

With the optimized conditions established, the substrate scope for thiophenes was first evaluated (Scheme 2). In the presence of 2.2 equivalents DMSO and HBr, various 3-arylthiophenes **2** were obtained in moderate to good yields. For instance, 2-phenylallyl alcohol with weak electron-donating substituents, such as Me, ^tBu, and Cy at the *para* position of phenyl ring, all reacted smoothly under the current condition and gave **2b–2e** in moderate yields (49–54%). Notably, halides, including fluoro, chloro, bromo, and iodo were well tolerated, delivering corresponding products **2f–2i** in 65–74% yields. Substituents at *meta* and *ortho* position of the phenyl ring were amenable to the transformation as well (**2j**, **2k**). It is noteworthy that naphthyl-substituted allyl alcohols could deliver the target products **2l**, **2m** in satisfactory yields as well. Allylic alcohol with polar functional group couldn't be transformed to thiophene effectively (**2n**). However, dihydrothiophene **4n** was observed as major product (35% yield). With respect to the alkyl substituted allylic

Table 1: Optimization of reaction conditions.^[a]

Entry	[Br]	Solvent	T [°C]	Conc. [M]	Yield [%] ^[b]		
					2a	3a	4a
1	HBr	toluene	100	0.20	8	–	8
2	HBr	dioxane	100	0.20	15	–	20
3	HBr	DMSO	100	0.20	–	–	–
4	HBr	CH ₃ NO ₂	100	0.20	56	–	–
5	HBr	CH ₃ NO ₂	120	0.20	60	–	–
6	HBr ^[c]	CH ₃ NO ₂	120	0.20	63	–	–
7	HBr ^[c]	CH ₃ NO ₂	120	0.10	68	–	–
8	HBr ^[c]	CH ₃ NO ₂	120	0.05	55	–	–
9	Py·HBr	CH ₃ NO ₂	120	0.10	–	–	–
10	Et ₃ N·HBr	CH ₃ NO ₂	120	0.10	–	–	–
11 ^[d]	HBr ^[c]	CH ₃ NO ₂	120	0.10	72	–	–
12 ^[e]	HBr ^[c]	CH ₃ NO ₂	120	0.10	2	63	–
13 ^[f]	HBr ^[c]	DCE	120	0.10	14	–	43

[a] Conditions: **1a** (0.20 mmol), DMSO (0.44 mmol), HBr (40%, 0.44 mmol), solvent, T [°C], 12 h. [b] Determined by GC-FID with mesitylene as the internal standard. [c] 33 wt% in acetic acid. [d] KBr (0.40 mmol) was used as an additive. [e] After 12 h, additional DMSO (0.22 mmol) and HBr (33%, 0.22 mmol) were added. The reaction mixture was then heated at 60 °C for 6 h. [f] DMSO (0.20 mmol), HBr (33%, 0.40 mmol).



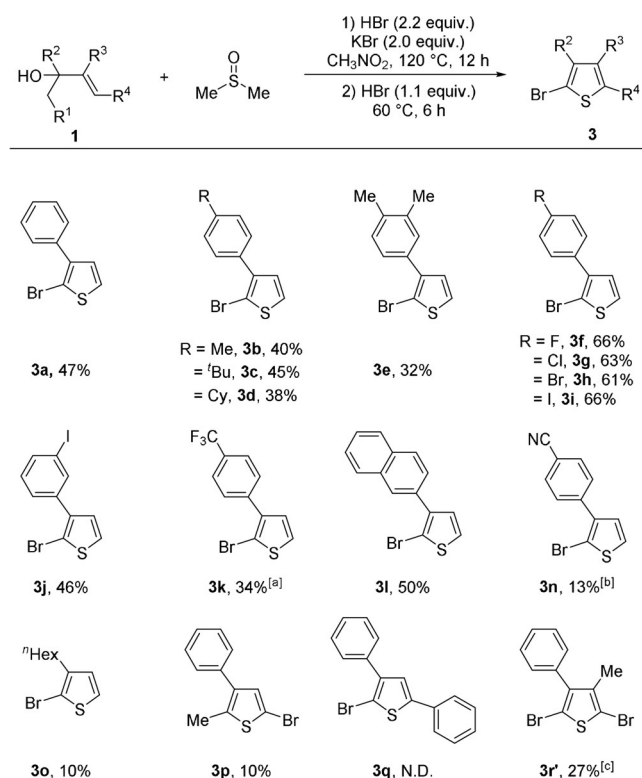
Scheme 2. Synthesis of 3-arylthiophenes. Conditions: **1** (0.20 mmol), DMSO (0.44 mmol), HBr (33%, 0.44 mmol), KBr (0.40 mmol), CH₃NO₂ (2.0 mL), 120 °C, 12 h. Isolated yields are given. [a] Determined by ¹H NMR analysis with mesitylene as the internal standard.

alcohol, the desired product was obtained with low yield (**2o**). Only a trace amount of product **2p** was observed when methyl group was introduced onto R¹ position. The alkene bears aryl group on terminal site delivered no target product (**2q**). However, the substitution on the internal site of alkene is tolerated (**2r**).

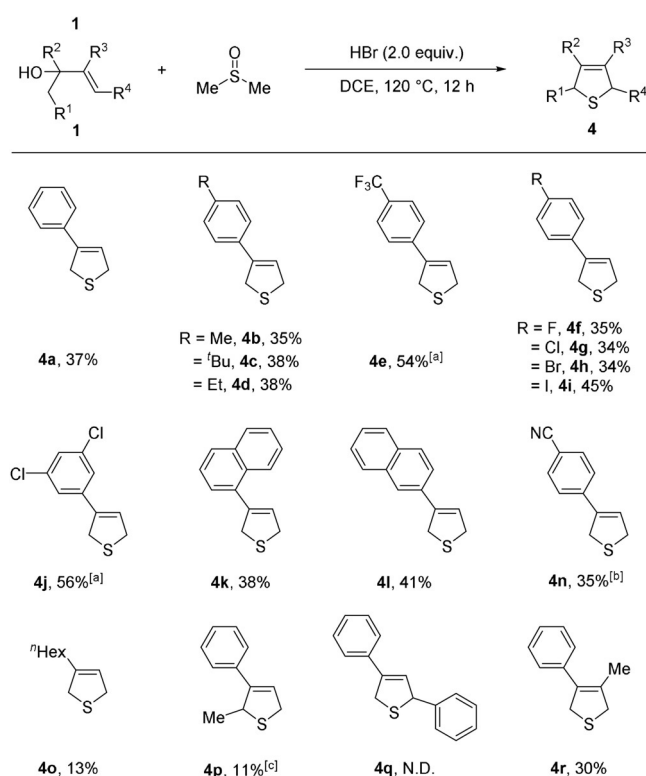
Next, we shifted our attention to explore the substrate scope of brominated thiophenes (Scheme 3). The reaction could be carried out with a series of allylic alcohols with different substituents on the aryl ring. It was observed that electron-donating substrates (**3b–3e**) gave slightly decreased yields in this case. However, substrates bearing halides, such as F, Cl, Br and I, were readily converted to the corresponding 2-bromo substituted thiophenes in 46–66% yields (**3f–3j**). Strong electron-withdrawing group CF₃ was also applicable under the current reaction conditions (**3k**). Moreover, the naphthyl substituted allylic alcohol was tested in this process, leading to 2-brominated thiophene **3l** in 50% yield. Substrate with a polar functional group (cyano) provided brominated thiophene with lower yield (**3n**). Alkyl substituted allylic alcohol could also be transformed to target product (**3o**). The introducing of methyl group onto R¹ position caused a decrease of yield (**3p**). The alkene bears aryl group on terminal

site didn't work in this protocol (**3q**). Interestingly, dibrominated thiophene product was obtained with a methyl group on the internal site of alkene (**3r**). In general, the substrate tolerance for the 2-bromo-3-aryl thiophenes is consistent with that for 3-arylthiophene (Scheme 2 vs. 3). It is worth noting that other regioisomers of brominated thiophene were not observed. This high regioselectivity of bromination probably resulted from the higher nucleophilicity of C2 position on 3-arylthiophene and low concentration of Br₂ that was generated in situ.^[24b]

Through decreasing the equivalents of mild oxidant DMSO and HBr, the scope generality for the redox selectivity switch towards dihydrothiophenes was investigated (Scheme 4). The reactions of substrates with electron-donating (**4b–d**) and -withdrawing substituents (**4e–i**) at the *para* position of the benzene ring all proceeded smoothly to give dihydrothiophene products in decent yields. Substituents at the *meta* position of phenyl ring of allylic alcohol also exerted moderate reactivity (**4j**). Substrates with naphthyl group, no matter located at the α - or β -position, were both suitable and produced the desirable product in 38% and 41% yield, respectively (**4k, 4l**). In general, the yields of dihydrothiophenes are comparably lower than thiophenes, which can be attributed to the difficulties in suppressing oxidation of dihydrothiophene to corresponding thiophene. The introduc-



Scheme 3. Synthesis of 2-bromo-3-arylthiophenes in one pot. Conditions: **1** (0.20 mmol), DMSO (0.44 mmol), HBr (33%, 0.44 mmol), KBr (0.40 mmol), CH₃NO₂ (2.0 mL), 120 °C, 12 h, then DMSO (0.22 mmol), HBr (33%, 0.22 mmol), 60 °C, 6 h. Isolated yields are given. [a] DMSO (0.40 mmol) and HBr (33%, 0.40 mmol) were used in the second step. [b] Accompanied by inseparable thiophene product, the yield of the product has been adjusted according to ¹H NMR analysis. [c] Accompanied by inseparable monobromination product, the yield of the product has been adjusted according to ¹H NMR analysis.



Scheme 4. Synthesis of 2-substituted 2,5-dihydrothiophenes. Conditions: **1** (0.20 mmol), DMSO (0.20 mmol), HBr (33%, 0.40 mmol), DCE (2.0 mL), 120 °C, 12 h, under N₂. Isolated yields are given. DCE = 1,2-dichloroethane. [a] DMSO (0.32 mmol), HBr (33%, 0.48 mmol), CH₃NO₂ (2.0 mL). [b] DMSO (0.44 mmol), HBr (33%, 0.44 mmol), CH₃NO₂ (2.0 mL). [c] Determined by ¹H NMR analysis with mesitylene as the internal standard.

tion of a cyano group on the aryl group of allylic alcohol provided the corresponding product in 35 % yield (**4n**). In addition, alkyl substituted allylic alcohol could afford the target product (**4o**). Only a small amount of dihydrothiophene was observed through the introducing of methyl group onto R¹ position (**4p**). Substrate with phenyl group on terminal site of alkene couldn't be transformed to product (**4q**). To our delight, substrate with a methyl group on the internal site of alkene was tolerated (**4r**). Due to the decrease of DMSO, some amount of unreacted diene was observed after workup. Furthermore, small amount of side product from Diels–Alder cycloaddition of diene was also detected under this protocol.

To unveil the mechanistic details of this established protocol, several control experiments were thereby performed (Scheme 5). When subjecting 2-phenyl-1,3-butadiene (**5a**) rather than 2-phenylbut-3-en-2-ol (**1a**) to the standard reaction conditions, 3-phenyl-thiophene (**2a**) could also be obtained in 72 % yield (Scheme 5a). This suggests that diene **5a** might be an intermediate for the formation thiophene **2a**. According to previous reports,^[24,26] DMSO could react with HBr to produce dimethyl sulfide (DMS) and Br₂. To test such process whether occurred in this protocol or not, the reaction between diene **5a** and DMS in the presence of Br₂ was conducted (Scheme 5b). The result showed that 69 % yield of **2a** could be delivered, indicating that DMS and Br₂ may be the active intermediates enrolled in the formation of **2a**. In addition, it was also found that 3-phenyl-thiophene **2a** could be obtained in 72 % yield from the oxidation of dihydrothiophene **4a** with the aid of DMSO and HBr (Scheme 5c). Notably, 34 % yield of trimethylsulfonium bromide **6** was observed as a side-product under the optimal conditions (Scheme 5d). This observation implies MeBr is the other destination for the methyl groups on DMSO.

The kinetic studies were further carried out to interpret the reaction process. As shown in Figure 1, the diene intermediate **5a** was quickly formed at the early stage of

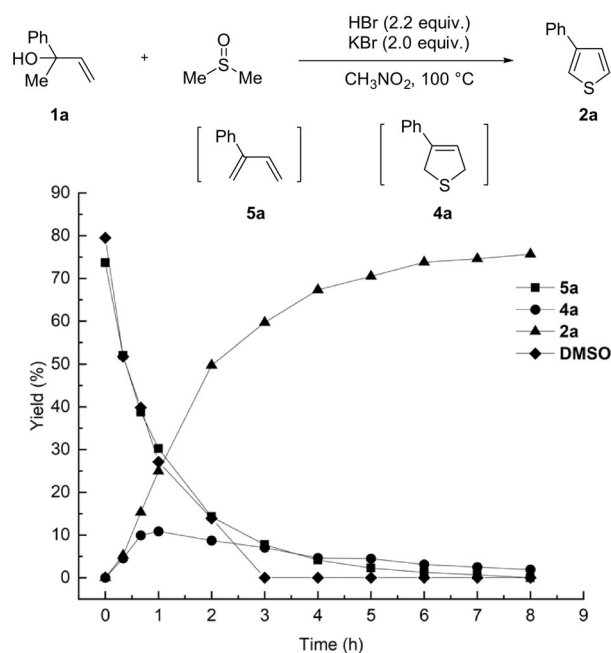
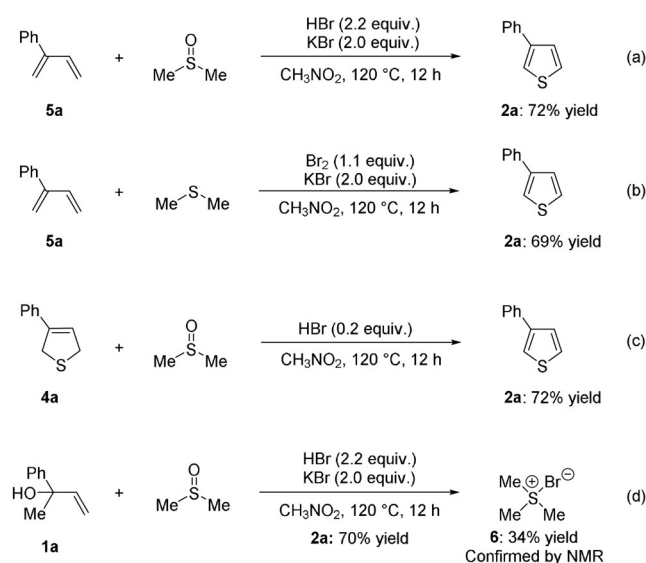


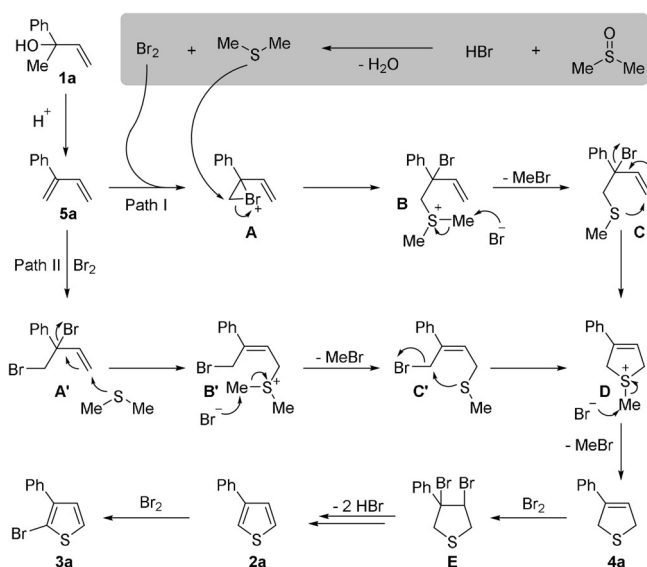
Figure 1. Kinetic studies of this synthesis.

the reaction and was continuously consumed as the reaction ongoing. In addition, a volcano-shaped correlation was observed between the yield of dihydrothiophene **4a** and the reaction time, while a sigmoidal kinetic curve was found for the desired thiophene **2a**. In addition, the trend of decrease of DMSO is consistent with **5a**. These results were in accordance with the above control experiments (Scheme 5a and c) which suggests that diene **5a** is a probable intermediate of the reaction and can be converted into dihydrothiophene **4a** and furthermore, thiophene **2a**.

On the basis of the aforementioned observations and previous reports,^[24,26,27] a plausible mechanism for this DMSO-based redox-divergent construction of (dihydro)thiophenes was shown in Scheme 6. Initially, an acid and thermal-induced dehydration of allylic alcohol **1a** produces the diene product **5a**. Meanwhile, the Br₂ and DMS are generated from the oxidation of HBr by DMSO.^[28] Next, the reaction between diene **5a** and Br₂ gives bromonium ion **A**, which then undergoes nucleophilic attack by DMS to afford the sulfonium ion **B** (Path I). A subsequent nucleophilic substitution of intermediate **B** with bromide anion releases the MeBr species and generates sulfide **C**. A further intramolecular nucleophilic substitution yields cyclic sulfonium salt **D**. An alternative pathway for the formation of intermediate **D** includes dibromination of alkene (**A'**) and subsequent inter-/intramolecular nucleophilic substitutions (Path II). A final reaction between intermediate **D** and bromide anion produces the dihydrothiophene product **4a**. In the presence of excess Br₂, intermediate **E** can be yielded through the bromination of **4a**. Subsequent elimination of HBr from the **E** gives thiophene **2a**. In the end, further bromination of **2a** with Br₂ produces 2-bromothiophene **3a** in an oxidative fashion.



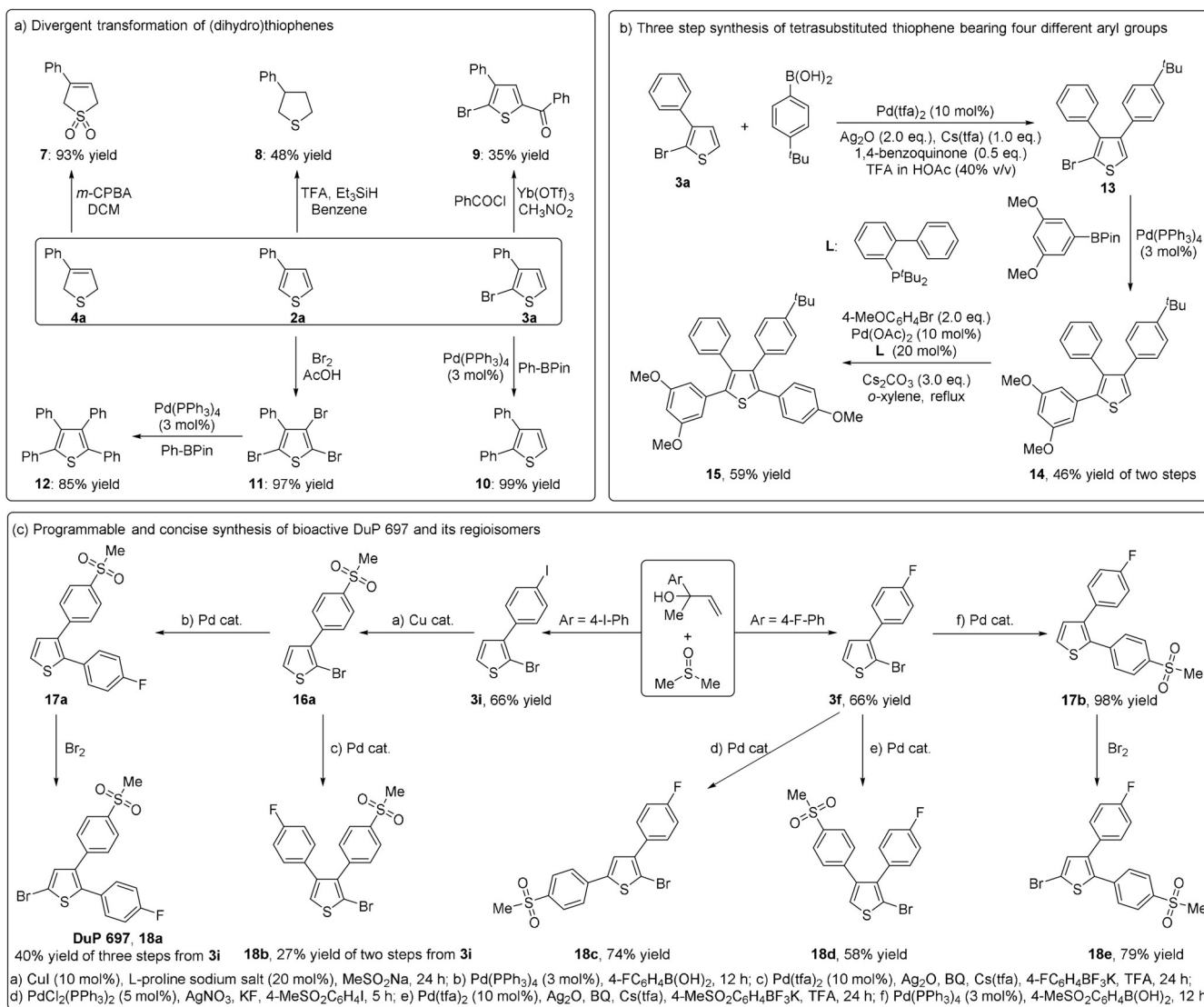
Scheme 5. Control experiments.



Scheme 6. Proposed redox-divergent mechanism for the synthesis of (dihydro)thiophene.

The synthetic utility of current protocol was demonstrated by diverse derivatizations of the obtained (dihydro)thiophene products **2a–4a** (Scheme 7). As illustrated in Scheme 7a, oxidation of **4a** with *m*-CPBA could readily give sulfolene **7** in 93% yield. In the presence of triethylsilane and triethylthiophene **2a** could be reduced to tetrahydrothiophene **8** in an acceptable yield.^[29] A bromination of **2a** with Br₂ successfully provided 2,3,5-tribromo-4-phenylthiophene **11** in 97% yield. To our delight, the obtained polybrominated thiophene **11** could be further functionalized through Suzuki–Miyaura cross-coupling to enable a rapid assembly of tetraphenylthiophene **12** (85% yield). For the transformation of **3a**, an acylative reaction with benzoyl chloride generated trisubstituted thiophene **9**. On the other hand, the Pd-catalyzed cross-coupling reaction of **3a** with phenylboronate efficiently delivered disubstituted thiophene **10** with excellent yield (99%).

Tetraarylthiophenes with four totally different aryl groups are privileged structures and useful building blocks in material chemistry.^[30] However, the synthetic access to such



Scheme 7. Divergent and programmable synthetic transformations of (dihydro)thiophenes.

skeletons is challenging and usually requires multiple steps (5–6 steps).^[30a,b] With brominated arylthiophene **3a** in hand, we could easily synthesize the triarylthiophene **14** in 46% yield (for two steps) via the continuous Suzuki-type C–H/C–Br arylation under palladium catalysis. After a final Pd-catalyzed C–H arylation with bromoarene, a new tetra-arylthiophene **15** with four different aryl groups could be prepared in high efficiency (3 steps, 27.1% overall yields, Scheme 7b).

With respect to bioactive molecules, DuP 697 (**18a**) and analogs were difficult to obtain via the traditional methods which need five steps at least.^[31] To further demonstrate the practicability of this redox-divergent strategy, bioactive DuP 697 and its regioisomers were programmatically and concisely synthesized from brominated thiophenes **3i** and **3f**. Firstly, **3i** could be easily transformed to **16a** through a CuI-catalyzed coupling reaction.^[32] Then, DuP 697 (**18a**) could be obtained in 40% yield through Pd-catalyzed Suzuki–Miyaura cross-coupling with arylboronic acids, followed by bromination of the diarylthiophene **17a**. Under Pd catalysis,^[33] **16a** was coupled with potassium aryltrifluoroborate to give **18b** in 27% yield (two steps from **3i**). Another DuP 697 regioisomer **18c** could be easily accessed (74% yield) through Pd-catalyzed C–H arylation at the C5 position of brominated thiophenes **3f** with aryl iodide.^[34] Under the condition for the direct C3 C–H arylation, **18d** can be produced between the cross coupling between thiophene **3f** and potassium aryltrifluoroborate. This one step synthesis represents the shortest synthesis for **18d**. Finally, **3f** were cross-coupled with arylboronic acids in the presence of Pd(PPh₃)₄ catalyst to afford **17b** in excellent yield, which could be easily brominated with bromine to give the last DuP 697 regioisomer **18e**.

Conclusion

In conclusion, we have established a redox-divergent strategy for the selective construction of substituted thiophenes or dihydrothiophenes under metal-free conditions. This protocol employed readily available allylic alcohols as starting materials and DMSO as mild oxidant to offer derivatives of (dihydro)thiophenes efficiently. Manipulation of the selectivity could be governed by the dosage of DMSO and HBr. Mechanistic investigations were conducted to interpret the redox selectivity and the roles of DMSO. In addition, synthetic transformations demonstrated that this strategy could realize programmable and concise synthesis of tetraarylthiophenes, bioactive DuP 697 and its regioisomers. Thus, this redox-divergent strategy may serve as a general platform for achieving synthetically and medicinally useful five-membered sulfur-containing heterocycles.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: bromothiophenes · dihydrothiophenes · dimethyl sulfoxide · redox-divergent synthesis · thiophene

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