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Transition-Metal-Free Sulfuration/Annulation of Alkenes: Economical Access to Thiophenes Enabled by the Cleavage of Multiple C−H Bonds

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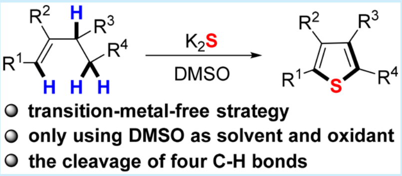
Supporting Information

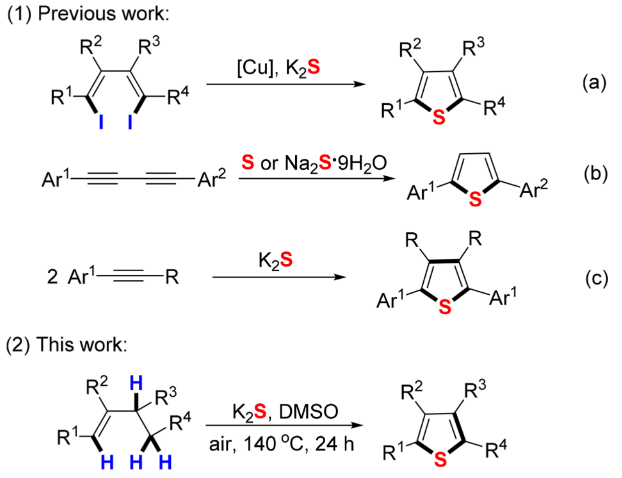
ABSTRACT: A novel, atom economical, and transition-metal-free strategy for the synthesis of thiophenes from substituted buta-1-enes with potassium sulfide has been presented. The reaction achieves double C−S bond formations via cleavage of multiple C−H bonds and provides an efficient approach to access various functionalized thiophenes. Moreover, the strategy can also be used for the synthesis of thiophenes from 1,4-diaryl-1,3-dienes. Mechanistically, DMSO plays a role of oxidant and $S_3^{\bullet-}$ in situ generated from K_2S is involved.



In recent decades, the sulfuration reaction of functionalized substrates by use of inorganic sulfurating reagents has emerged as a powerful tool to assemble sulfur-containing heterocycles.[1−4] In particular, the C−H bond sulfuration reaction has attracted increasing attention in recent years due to atom economy and the avoidance of prefunctionalization of the starting materials, and significant progress has already been made toward the preparation of sulfur-containing heterocycles.[3] However, on the one hand, such successful examples remain scarce. On the other hand, these approaches have focused on the sulfuration of $C(sp^2)$−H bond and activated $C(sp^3)$−H bonds adjacent to the nitrogen atom or double bond. Thus, the direct sulfuration of an inert $C(sp^3)$−H bond adjacent to the alkyl carbon for the construction of sulfur-containing heterocycles is not reported and even more challenging.

The synthesis of thiophenes is interesting to scientific researchers[4,7,8] as they represent an important class of sulfur-containing heterocycles, which are ubiquitous core structural motifs found in natural products, pharmaceuticals,[5] and functional materials.[6] Recently, several efficient methods for the synthesis of thiophenes have been developed through the coupling annulation of 1,4-diiodo-1,3-dienes with potassium sulfides (Scheme 1-1a)[7] or the sulfuration/annulation of 1,3-diynes and arylacetylenes with inorganic sulfurating reagents such as elemental sulfur, potassium sulfide, and sodium sulfide (Scheme 1-1b and -1c)[8] by the groups of Xi, Lei, Jiang, Ji, and so on. However, the method which employs inorganic sulfurating reagents to prepare thiophenes via C−H bond functionalization is urgently needed. Very recently, we have established the C−H bond sulfuration of easily available N-substituted arylamines for the synthesis of benzothiazoles under transition-metal-free conditions.[9] The method enabled the cleavage of one $C(sp^2)$−H bond and two $C(sp^3)$−H bonds adjacent to the nitrogen atom. Accordingly, as a part of our ongoing interests toward developing efficient methods for building sulfur-containing heterocycles,[10] the results have led us to investigate the possibility for synthesis of thiophenes via a similar strategy. Fortunately, functionalized thiophenes could be synthesized from readily available substituted buta-1-enes via the cleavage of multiple C−H bonds, including two inert $C(sp^3)$−H bonds adjacent to alkyl carbon, one $C(sp^3)$−H bond adjacent to double bond, and one $C(sp^2)$−H bond (Scheme 1-2). Herein, we wish to detail our results.

Scheme 1. Synthesis of Thiophenes Enabled by Inorganic Sulfurating Reagents



We commenced with the sulfuration/annulation reaction of 1,3-diphenyl-1-butene **1a** and K_2S for exploring the optimal reaction conditions (Table 1). We were pleased to find that the

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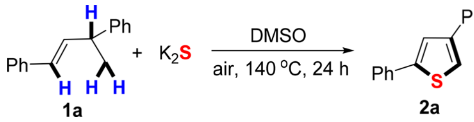
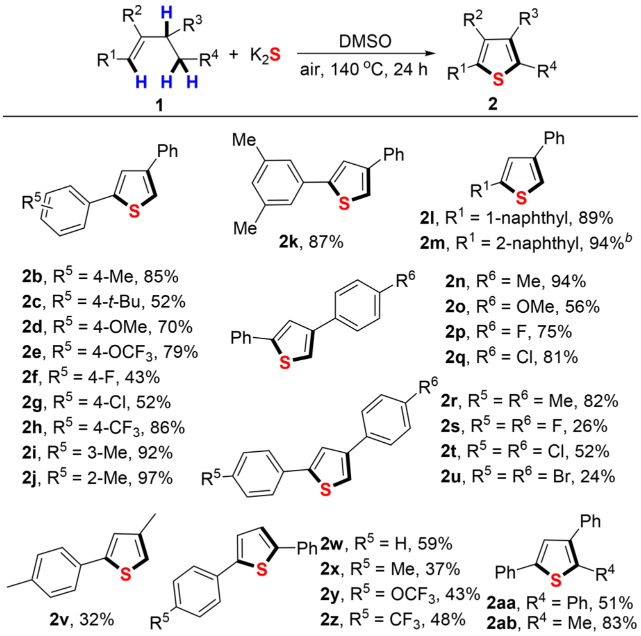
Table 1. Optimization of the Reaction Conditions[a]



entry	variation from the standard conditions	yield (%)[b]
1	none	93
2	Na_2S instead of K_2S	23
3	Li_2S instead of K_2S	51
4	S instead of K_2S	68
5	DMF instead of DMSO	54
6	NMP instead of DMSO	65
7	CH_3CN instead of DMSO	24
8	nitrogen instead of air	93
9	in 120 °C, for 60 h	94
10[c]	none	86

[a] Reaction conditions: **1a** (0.3 mmol), K_2S (0.9 mmol), and DMSO (2 mL) at 140 °C for 24 h under air. [b] Isolated yield. [c] **1a** (1 mmol).

Scheme 2. Variation of the Substituted Butenes 1[a]



[a] Reaction conditions: **1** (0.3 mmol), K_2S (0.9 mmol), and DMSO (2 mL) at 140 °C for 24 h under air. [b] 48 h.

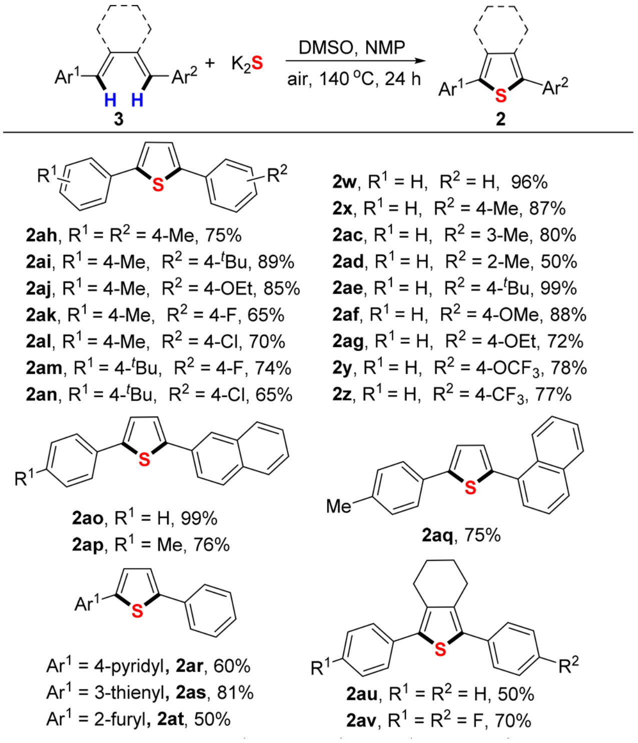
desired product **2a** could be obtained in 93% yield through simple heating to 140 °C in DMSO under transition-metal-free conditions. Other sulfur sources, namely Na_2S, Li_2S, and elemental sulfur, were subsequently screened, but all of them were inferior to K_2S (entries 2−4). The nature of solvents was found to affect the reaction, and the yields were dramatically decreased by replacing DMSO with DMF, NMP, or CH_3CN (entries 5−7). Under the nitrogen atmosphere, the reaction exhibited the identical activity (entry 8). When decreasing the temperature to 120 °C, the 2,4-diphenylthiophene could be given in 96% yield, but the reaction time needed to be extended to 60 h (entry 9). After comprehensive considerations on these results, the optimal conditions are as follows: **1a** (0.3 mmol) and K_2S (0.9 mmol) in DMSO (2 mL) at 140 °C for 24 h under air. Finally, the reaction scale up to 1 mmol of **1a** could provide **2a** in 86% yield (entry 10).

After identifying the optimal reaction conditions, we set out to investigate the substrate scope of this transition-metal-free sulfuration/annulation protocol (Scheme 2). We initially examined the compatibility of various functional groups on the aromatic ring of 1,3-diaryl butenes **1b−u**. Gratifyingly, the optimal conditions were compatible with a wide range of substituents, including electron-donating groups (Me, OMe, *t*-Bu, and OCF_3) and electron-withdrawing groups (F, Cl, Br, and CF_3). For most of the 1,3-diaryl butenes **1b−e** and **1h−r**, the sulfuration/annulation protocol proceeded smoothly, and the corresponding 2,4-diaryl thiophenes (**2b−e** and **2h−r**) were obtained in good to excellent yields. To this reaction, the steric effect of the substituents was not obvious. For example, the *para-*, *meta-*, and *ortho*-methylphenyl substituted thiophenes (**2b**, **2i**, and **2j**) were afforded in 85%, 92%, and 97% yields, respectively. Importantly, 1-methyl-4-(3-methylbut-1-en-1-yl)benzene **1v** could successfully be converted into the desired product **2v**, albeit with a diminished yield. Subsequently, the sulfuration/annulation protocol was applicable to 1,4-diaryl substituted butenes **1w−z**, and 2,5-diaryl substituted thiophenes **2w−z** were afforded in moderate yields. In addition, it was noted that 2,3,5-trisubstituted thiophenes (**2aa** and **2at**) were synthesized in 51% and 83% yields, respectively.

Based on the successful sulfuration/annulation strategy of alkenes, we speculated that the reaction possibly underwent a diene intermediate, which could deliver the desired product by a double C−H bond sulfuration process. Therefore, 1,4-diphenyl-1,3-dibutene **3w** was subjected to the sulfuration/annulation reaction with K_2S under the above standard reaction conditions. Expectedly, 2,5-diphenylthiophene **2w** was obtained in 82% yield. Further survey revealed that the yield of 2,5-diphenylthiophene increased to 96% when the mixture solvent DMSO and NMP in a ratio of 1:1 was used. Encouraged by this results, the scope of the sulfuration/annulation reaction with regard to 1,4-diaryl-1,3-dibutenes (**3x-z** and **3ac-at**) was then examined (Scheme 3). An array of substrates (**3x-z** and **3ac-an**) with substituents on the aromatic ring Ar^2 or both of the aromatic rings Ar^1 and Ar^2 could uneventfully be translated into the conrresponding products (**2x-z** and **2ac-an**) in moderate to excellent yields. It was noteworthy that the steric effect of the substituent was obvious in this reaction. For example, the *para-*, *meta-*, and *ortho*-methylphenyl substituted thiophenes (**2x**, **2ac**, and **2ad**) were afforded in 87%, 80%, and 50% yields, respectively. Furthermore, polycyclic naphthyl, heterocyclic pyridyl, and thienyl substituted 1,3-dibutenes **3ao-at** were competent substrates for the sulfuration/annulation reaction. Interestingly, fully substituted 1,3-diaryl-4,5,6,7-tetrahydrobenzo[*c*]-thiophenes **2au** and **2av** were also synthesized in moderate yields.

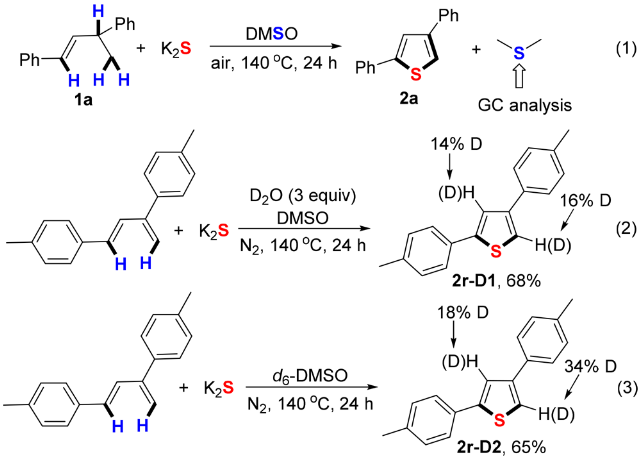
To investigate the possible reaction mechanism, several control experiments were carried out (Scheme 4). The reaction of 1,3-diphenyl-1-butene (**1a**) and K_2S detected the production of dimethyl sulfide by GC analysis under the standard conditions (eq 1; see the Supporting Information (SI)). The result reveals that DMSO could play a vital role of oxidant in the sulfuration/annulation process.[9,11] The results of the isotope experiments indicate that both solvent (DMSO) and water could act as a hydrogen donor, which participated in the reaction (eqs 2 and 3). Therefore, we speculated that two types of H-abstraction, including proton-hydrogen capture[8a]

Scheme 3. Variation of the 1,4-Diaryl-1,3-dibutaenes 3[a]



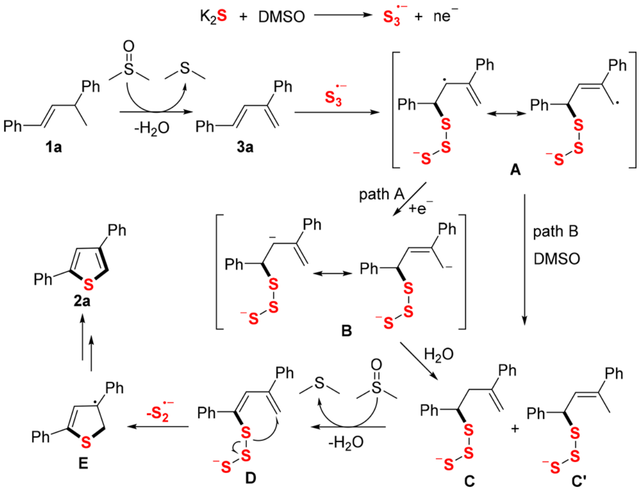
[a] Reaction conditions: **3** (0.3 mmol), K_2S (0.9 mmol), and DMSO (2 mL) at 140 °C for 24 h under air.

Scheme 4. Control Experiment



and radical-hydrogen capture,[8c] occurred in the transformation.

Scheme 5. Possible Reaction Mechanism



Based on the previous reports, the $S_3^{\bullet-}$ species, which can be produced by the reaction of elemental sulfur and base or inorganic sulfides in DMF or DMA, was initially discovered by Chivers and Shields.[12] Recently, Lei and Ji et al. developed several methods involving $S_3^{\bullet-}$species for the synthesis of sulfur-containing heterocycles.[2d,8a−c] Herein, our electron paramagnetic resonance (EPR) study reveals that this reaction possibly involved $S_3^{\bullet-}$ in situ generated from K_2S (see the SI). Therefore, a hypothetical reaction mechanism involving $S_3^{\bullet-}$species for the synthesis of thiophenes was proposed based on the reported literature and our experimental results (Scheme 5). First, oxidative dehydrogenation of 1,3-diphenyl-1-butene **1a** affords 1,3-diphenyl-1,3-dibutene **3a** with the aid of DMSO. Subsequently, radical addition of $S_3^{\bullet-}$ in situ generated from K_2S to **3a** provides the intermediate **A**, which undergoes two reaction pathways to form the intermediate **C** and **C′** (path A: sequential getting an electron and proton-hydrogen capture; path B: radical-hydrogen capture). Under the action of DMSO, the second oxidative dehydrogenation of intermediate **C** and **C′** delivers the intermediate **D**, which undergoes intramolecular radical addition to obtain the intermediate **E** and release $S_2^{\bullet-}$. Finally, the thiophene **2a** is produced via sequential H-abstraction and further oxidation of intermediate **E**. Furthermore, another pathway involving radical addition of $S_3^{\bullet-}$ to the 4-position of **3a** is not ruled out (for the detailed mechanism, see the SI).

In conclusion, we have described a transition-metal-free strategy for the synthesis of thiophenes from substituted buta-1-enes and potassium sulfide. The method provides straightforward access to diverse functionalized thiophenes in moderate to excellent yields through cleavage of three types of C−H bonds such as two inert C(sp^3)−H bonds adjacent to the alkyl carbon, one C(sp^3)−H bond adjacent to the double bond, and one C(sp^2)−H bond. Furthermore, the method can be applicable to 1,4-diaryl-1,3-dibutenes for assembling functionalized thiophenes by a slight change in the optimal reaction conditions. Further mechanistic studies and applications of this method are currently in progress in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03078.

Experimental procedures, full characterization of products, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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