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Trisulfur Radical Anion ($S_3^{\bullet-}$) Involved Sulfur Insertion Reaction of 1,3-Enynes: Sulfide Sources Control Chemoselective Synthesis of 2,3,5-trisubstituted Thiophenes and 3-thienyl Disulfides†

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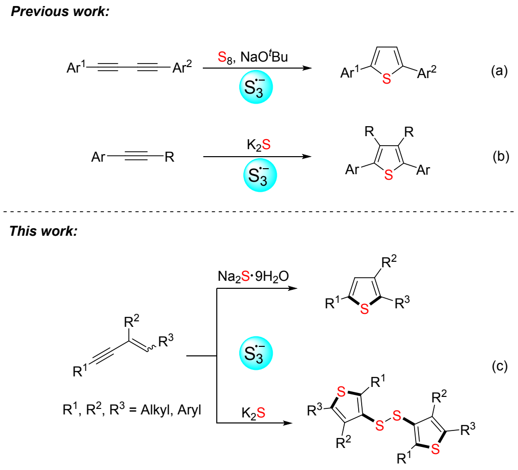
Cascade cyclization reactions of $S_3^{\bullet-}$ in situ generated from S^{2-} with 1,3-enynes for the chemoselective synthesis of 2,3,5-trisubstituted thiophenes and 3-thienyl disulfides controlled by sulfide slats are developed. These two protocols provide new, environment-friendly and simple strategies to construct 2,3,5-trisubstituted thiophenes and 3-Thienyl disulfides *via* two and six C-S bond formations, respectively.

Disulfides are important building blocks in organic synthesis. They can be used as precursors of nucleophilic reagents or radicals to participate in lots of organic synthesis reactions by S-S bond heterolytic or homolytic cleavage.[1] Thiophenes are basic skeletons found in new electronic materials[2] as well as in biologically active molecules.[3] And the thiophene group can be directly introduced into the target molecule through the C-S bond construction reaction involving dithienyl disulfide, which is an important method for modifying the molecule in the field of medicine and materials.

Although $S_3^{\bullet-}$ species has been known for more than 40 years,[4] applications of this reactive species in organic synthesis are getting more and more attention until recent years.[5] Several efficient methods for the synthesis of thiophenes have been developed through the coupling annulation of reactants with $S_3^{\bullet-}$ in situ generated from some inorganic sulfurating reagents.[6] Lei's group reported an S_8 and base in situ generated $S_3^{\bullet-}$-mediated [4+1] cyclization with 1,3-diynes for synthesis of 2,5-diarylthiophenes (Scheme 1a).[6a] More recently, our group developed an in situ generated $S_3^{\bullet-}$ from a K_2S-initiated [1+2+2] cycloaddition reaction with phenylacetylenes to afford tetra-substituted thiophenes (Scheme 1b).[6d] Herein, we describe a $S_3^{\bullet-}$ in situ generated from S^{2-}-mediated involved sulfur insertion reaction with 1,3-enynes[7,8] to give 2,3,5-trisubstituted thiophenes and 3-thienyl disulfides chemoselectively controlled by sulfide salts[9] (Scheme 1c).



Scheme 1 Applications of $S_3^{\bullet-}$ in thiophenes synthesis

Initially, we investigated the reaction of but-1-en-3-yne-1,2,4-triyltribenzene **1aa** and K_2S **2a** in DMF at 130 °C for 7 h under Ar atmosphere. To our surprise, 1,2-bis(2,4,5-triphenylthiophen-3-yl)disulfane **4aa** was observed in 73% isolated yield besides the formation of [4+1] cyclization product 2,3,5-triphenylthiophene **3aa** in 24% isolated yield (Table 1, entry 1). Next, other sulfur reagents such as cyclo-S_8, $Na_2S·9H_2O$, $Na_2S_2O_3$, thiourea were applied in the reaction (Table 1, entries 2-5). It was found that different sulfur reagents have a huge impact on the selectivity of the reaction. When **1aa** reacted with $Na_2S·9H_2O$ under similar reaction conditions, only **4aa** was obtained in 87% isolated yield (Table 1, entry 2). The reaction of **1aa** with cyclo-S_8 (with NaO^{t}Bu) could also react smoothly to give **3aa** in 35% isolated yield and **4aa** in 21% isolated yield (Table 1, entry 3). There was no reaction when $Na_2S_2O_3$ and thiourea were applied in the reaction (Table 1, entries 4-5).

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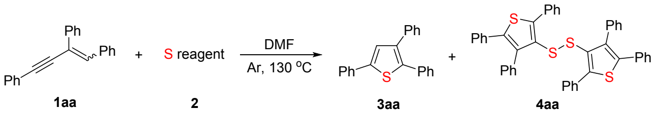
Table 1 Sulfur reagents controlled synthesis of **3aa** and **4aa**[a]



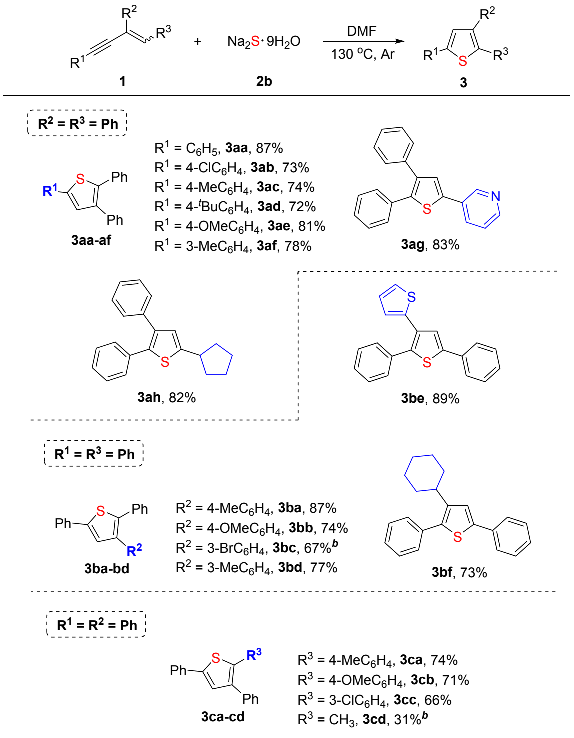
entry	S reagent	yield[b] (%)	
		3aa	4aa
1	K_2S	24	73
2	$Na_2S{\cdot}9H_2O$	87	<3
3	S_8 + NaO^{t}Bu	35	21
4	$Na_2S_2O_3$	0	0
5	Thiourea	0	0

[a]Reaction conditions: **1aa** (0.3 mmol), **2** (1.2 mmol), DMF (2.0 mL), 130 °C, under Ar, 7 h. [b]Isolated yield.

Based on the above experimental results, it was found that $Na_2S{\cdot}9H_2O$ could be applied in the reaction to obtain 2,3,5-trisubstituted thiophenes and K_2S could be applied in the reaction to obtain 3-thienyl disulfides. With this promising result in hand, we further screened the reaction conditions (solvents, temperature and time) to optimize the two reactions (see supporting information (SI) for more details).

With the established reaction conditions in hand, we explored the substrate scope of 1,3-enynes for the two reactions. The libraries of 2,3,5-trisubstituted thiophenes and 3-thienyl disulfides are shown in Table 2 and Table 3, respectively.

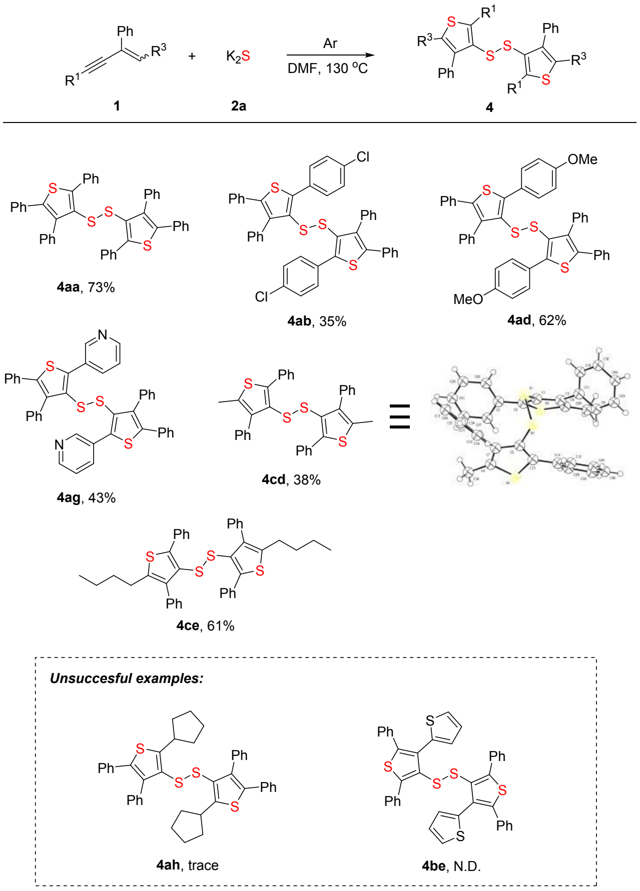
Table 2 Synthesis of 2,3,5- trisubstituted thiophenes[a]



[a]Standard conditions: 1,3-enynes **1** (0.3 mmol), $Na_2S{\cdot}9H_2O$ **2b** (1.2 mmol), DMF (2.0 mL), at 130 °C, Ar, 7 h; Isolated yields were reported. [b]K_2S **2a** instead of $Na_2S{\cdot}9H_2O$ **2b**.

We examined the compatibility of various functional groups on the aromatic ring of enynes **1aa-af**, **1ba-bd**, and **1ca-cc** and the results are summarized in Table 2. Gratifyingly, the optimal conditions were compatible with a wide range of substituents, including electron-donating groups (Me, OMe, tBu) and electron-withdrawing groups (Cl, Br). For most of the aryl-substituted enynes **1aa-af**, **1ba-bd**, and **1ca-cc**, the cyclization reaction proceeded smoothly, and the corresponding 2,3,5-triaryl thiophenes (**3aa-af**, **3ba-bd**, and **3ca-cc**) were obtained in good yields. It should be noted that the reaction of 3-(3,4-diphenylbut-3-en-1-yn-1-yl)pyridine **1ag** and 2-(1,4-diphenylbut-1-en-3-yn-2-yl)thiophene **1be** with $Na_2S{\cdot}9H_2O$ could gave **3ag** and **3be** in 83% and 89% yields, respectively. Importantly, when the substituent groups (R^1, R^2, R^3) are alkyl groups, the reaction could also reacted smoothly. For example, When (4-cyclopentylbut-1-en-3-yne-1,2-diyl)dibenzene **1ah** was applied to reaction with **2a**, the desired product **3ah** was observed in 82% yield.

Table 3 Synthesis of 3-thienyl disulfides[a,b]



[a]Standard conditions: 1,3-enynes **1** (0.5 mmol), K_2S **2a** (2.0 mmol), DMF (2.0 mL), at 130 °C, Ar, 5 h; Isolated yields were reported.

As shown in Table 3, functional groups (Cl, OMe) on the aromatic ring of enynes **1aa**, **1ab**, **1ad** were well tolerated, giving 3-thienyl disulfides **4aa**, **4ab**, **4ad** in good isolated yields. It should be noted that the reaction of 3-(3,4-diphenylbut-3-en-1-yn-1-yl)pyridine **1ag** with K_2S could also furnish **4ag** in 43% yields. When the substituent groups R^3 are alkyl groups (**1cd**, **1ce**), the reaction could also react smoothly to give **4cd** and

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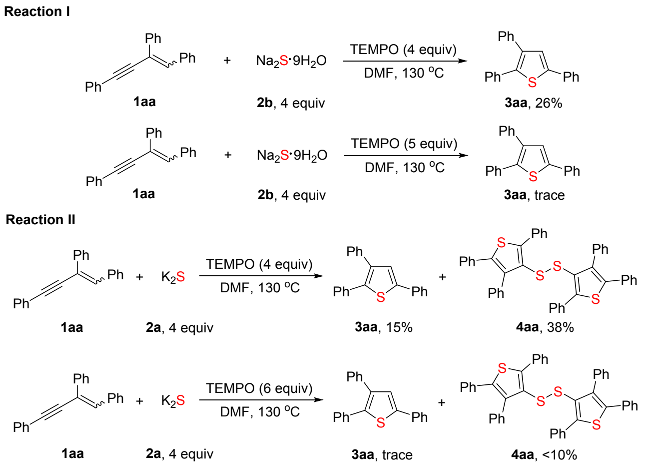
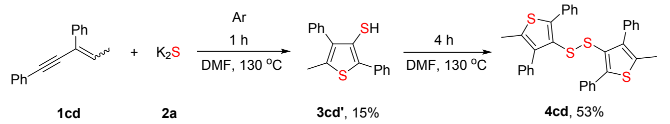
4ce in 38% and 61% yields, respectively. The structure of **4cd** was further confirmed by X-ray diffraction. Unfortunately, thiophene or cyclopentyl group substituted enynes failed to give the desired products **4ah** and **4be** under the optimized conditions.

To explore the plausible mechanism of these two reactions, radical-trapping experiments were performed (Scheme 2). When 4.0 equivalent of TEMPO was added to the reaction, the yields of **3aa** and **4aa** were reduced sharply. As the amount of TEMPO was increased to 5.0 equivalents and 6.0 equivalents respectively, these two reactions were almost fully suppressed. This observation indicated that a radical pathway might be involved in the reactions.



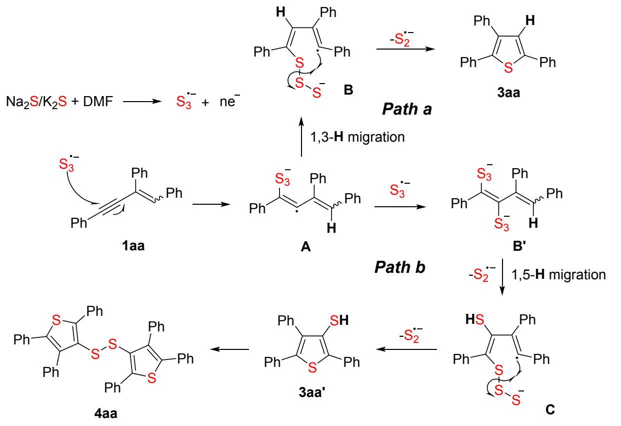
Scheme 2 Radical-trapping experiments.

To gain in-depth insight into the mechanism for the synthesis of 3-thienyl disulfides, some control experiments were carried out (Scheme 3). First, product 5-methyl-2,4-diphenylthiophene-3-thiol **3cd'** could be obtained in 15% isolated yield after pent-3-en-1-yne-1,3-diyldibenzene **1cd** reacted with K_2S under the standard condition for 1 hour. Then, 1,2-bis(5-methyl-2,4-diphenylthiophen-3-yl)disulfane **4cd** was obtained successfully after **3cd'** was put in DMF at 130 °C for another 4 hours. These results indicate that the thiophene-3-thiol might be an intermediate in reaction for the synthesis of 3-thienyl disulfides.



Scheme 3 Control experiments.

Based on the reported literatures[5b,6] and our experimental results (the deuterated experimental results could be seen in SI for more details), two reaction mechanisms were proposed in Scheme 4.[10] First, $S_3^{\bullet-}$ in situ generated from K_2S or Na_2S attacks the but-1-en-3-yne-1,2,4-triyltribenzene **1aa** to generate the radical anion intermediate **A**. In the generation of the 2,3,5-trisubstituted thiophenes (path a), the intermediate **A** converts to intermediate **B** by 1,3-hydrogen migration. The intramolecular radical coupling of **B** gives the cyclization product **3aa** *via* S-S bond homolysis and releasing $S_2^{\bullet-}$. For the synthesis of the 3-thienyl disulfides (path b), another $S_3^{\bullet-}$ reacts with intermediate **A** to form intermediate **B'**. The intermediate **B'** converts to intermediate **C** through S-S bond homolysis and 1,5-hydrogen migration. The intramolecular radical coupling of **B** gives intermediate **3aa'** *via* S-S bond homolysis and releasing $S_2^{\bullet-}$. Then, the intermediate **3aa'** is oxidized to form the disulfide product **4aa**.



Scheme 4 A plausible mechanism.

In summary, we have developed $S_3^{\bullet-}$ in situ generated from S^{2-} mediated cascade cyclization reactions with 1,3-enynes for the chemoselective synthesis of 2,3,5-trisubstituted thiophenes and 3-Thienyl disulfides controlled by sulphide salsts. These two protocols provides new, environment-friendly and simple strategies to construct 2,3,5-trisubstituted thiophenes and 3-thienyl disulfides *via* two and six C-S bond formations under transition metal-free conditions, respectively.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

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The syntheses and characterization of compounds **3ae**, **3ag**, **3ba**, **3be**, **3bf** and **4ce** were repeated and checked by Fei Wang in our group.

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10 The reaction mechanism of $Na_2S{\cdot}9H_2O$ involved in the synthesis of thiophenes is very complicated, and we illustrate a possible mechanism here.