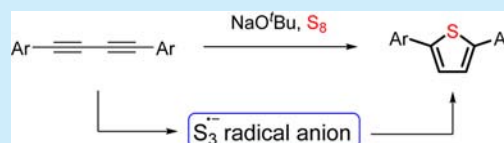


Trisulfur Radical Anion as the Key Intermediate for the Synthesis of Thiophene via the Interaction between Elemental Sulfur and NaOtBu

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S Supporting Information

ABSTRACT: A facile base-promoted sulfur-centered radical generation mode and a single-step protocol for the synthesis of thiophene derivatives using 1,3-diynes via the interaction between elemental sulfur and NaOtBu has been reported. EPR experiments revealed that the trisulfur radical anion acts as a key intermediate of this process. A plausible mechanism has been proposed.



The sulfur-centered radicals have received increasing attention, and a number of unique synthetic applications of S-radicals have been reported.¹ For instance, the radical-mediated thiol addition to alkynes has been used to prepare S-functionalized alkenes and to obtain kinetic data and some mechanistic insight into these reactions. Apart from thiyl radicals, thiocyanato (NCS·),^{1j} sulfonyl radicals (RSO₂·),² and pentafluorosulfanyl radicals (F₅S·)^{1b} have also been studied. However, the unfriendly radical initiators were usually essential in these reports. Therefore, a much milder radical initiator mode is highly desirable.

Recently, base promoted direct arylation of unactivated arenes with aryl halides through the homolytic aromatic substitution (HAS) pathway has gained much interest.³ This base-promoted radical initiator method is much milder and has been utilized in certain C–H activation reactions. Single-electron transfer (SET) between the *tert*-butoxide and aryl halides generates a radical or a radical anion in such a transformation.^{3d} As in the case of aryl halides, the elemental sulfur could also react with a base to generate radicals.⁴ In order to observe the interaction between the elemental sulfur and base, we have undertaken systematic EPR studies (Figure 1). Gratifyingly, a single Lorentzian line located at *g* = 2.0292 was observed when elemental sulfur was reacted with NaOtBu in DMF at room temperature (Figure 1b). In 1991, Lelieur also found the same EPR signal in the solution of sulfur in liquid ammonia, and they defined it as the trisulfur radical anion (S₃^{•-}).⁵ Also, this interaction could happen between the elemental sulfur and KOH (Figure 1a).⁶ However, the EPR signal would disappear when a weaker base, such as Na₂CO₃, was used (Figure 1d), or in the water solution (Figure 1c).

The trisulfur radical anion (S₃^{•-}) is well-known from inorganic chemistry textbooks as the blue chromophore in ultramarine blues.⁴ To the best of our knowledge, however, there was only one report available on carbon–sulfur bond formation via this reactive species.⁷ Although this blue radical anion is ubiquitous in our life, its application in organic or inorganic synthesis is still a huge challenge. Herein, we report a

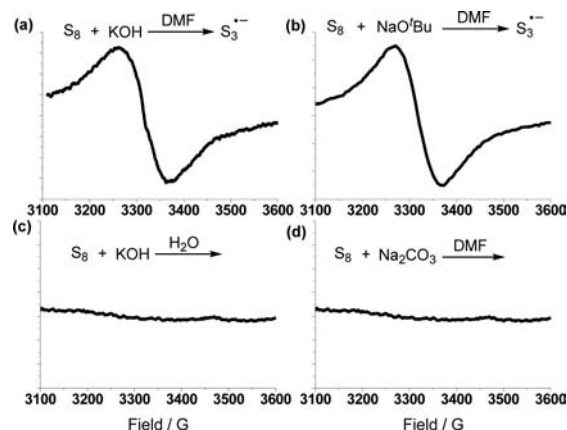


Figure 1. EPR studies of interaction between elemental sulfur and base.

base-promoted trisulfur radical anion generation, using it as the key intermediate for the synthesis of thiophene derivatives.

We began our study by tentatively investigating the interaction between the trisulfur radical anion and some unsaturated compounds.^{2,8} Delightfully, when we used 1,4-diphenylbuta-1,3-diyne **1a** to react with the elemental sulfur at room temperature under basic conditions, 2,5-diphenylthiophene **2a** could be found in 65% yield (Table 1, entry 1). After screening several bases and solvents, we found that this reaction is very sensitive to the base and solvent. Thiophene could be detected only under special and limited conditions, in which we could monitor the EPR signal of the trisulfur radical anion. For example, the product **2a** could be formed only in DMF, DMA, DMSO, and acetonitrile, in which the trisulfur radical anion (S₃^{•-}) was observed in some reports.^{4,9} To our delight, the use of 3.0 equiv of elemental sulfur and 6.0 equiv of NaOtBu in a 1:3 (v/v) mixture of *t*BuOH and DMF at 25 °C gave the

Received: October 13, 2014

Published: November 19, 2014

Table 1. Optimization of Reaction Conditions^a

$\text{Ph}-\text{C}\equiv\text{C}-\text{C}\equiv\text{C}-\text{Ph} + 1/8 \text{S}_8 \xrightarrow[\text{solvent, rt}]{\text{base}} \text{Ph}-\text{C}_4\text{H}_2\text{S}-\text{Ph}$			
entry	base	solvent	yield (%) ^b
1	NaOtBu	DMF	65
2	KOH	DMF	38
3	KOH	H ₂ O	n.d. ^c
4	Na ₂ CO ₃	DMF	n.d. ^c
5	NaOtBu	DMA	32
6	NaOtBu	DMSO	53
7	NaOtBu	CH ₃ CN	3
8	NaOtBu	toluene	n.d. ^c
9 ^d	NaOtBu	DMF	91(92)
10 ^e	KOH	DMF	83

^aReaction conditions: **1a** (0.30 mmol), sulfur powder (0.90 mmol), base (1.8 mmol), and in solvent (2.0 mL) at 25 °C in N₂.

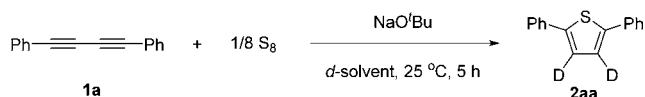
^bDetermined by GC using naphthalene as an internal standard; the yield in the parentheses is isolated yield. ^cn.d. = no desired product.

^dThe solvent was 1.5 mL of DMF and 0.5 mL of *t*BuOH, ^eThe solvent was 1.5 mL of DMF and 0.50 mL of EtOH.

desired product in 92% yield (Table 1, entry 9). It can also be noted that the use of KOH as the base and EtOH as the co-solvent also can give a good yield (Table 1, entry 10).

As shown in Scheme 1, the 2,5-diphenylthiophene, 4-*d*² **2aa** was formed when solvent was replaced by *d*⁶-DMSO. The GC-

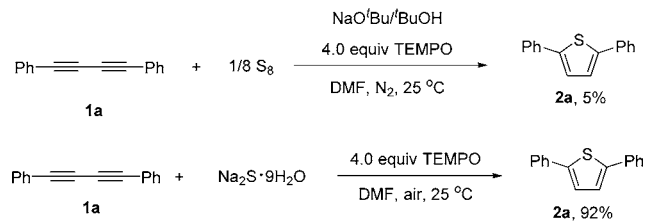
Scheme 1. Deuterated Experiment



MS spectrum showed an *m/z* signal at 238, which was attributed to the (M + 2)⁺ ion of **2a**. This result indicated that the solvent took part in this reaction and acted as the hydrogen donor in the transformation.

When we started investigating the reaction mechanisms, the radical addition pathway was an obvious consideration. Therefore, radical-trapping experiments were carried out (Scheme 2). When we added 4.0 equiv of TEMPO, the

Scheme 2. Radical-Trapping Experiments



reaction was almost fully inhibited. So this means that the reaction might involve a radical pathway. In 2013, Zhao and his co-workers developed a practical approach for the preparation of 2,5-disubstituted thiophenes via metal-free sulfur heterocyclization of 1,3-diynes with sodium hydrosulfide or sodium sulfide.¹⁰ To our surprise, the reaction proceeded smoothly under the standard conditions of Zhao's report when adding 4.0 equiv of TEMPO. This significant difference indicated that a

radical pathway is involved in our reaction and the trisulfur radical anion might be the key intermediate.

To gain some insights into the interaction between the elemental sulfur and sulfide or polysulfides, the electron paramagnetic resonance (EPR) experiment was carried out. A single EPR signal which was assigned to the trisulfur radical was observed in the DMF solution of Na₂S·9H₂O and the elemental sulfur at room temperature (Figure 2). The result showed that

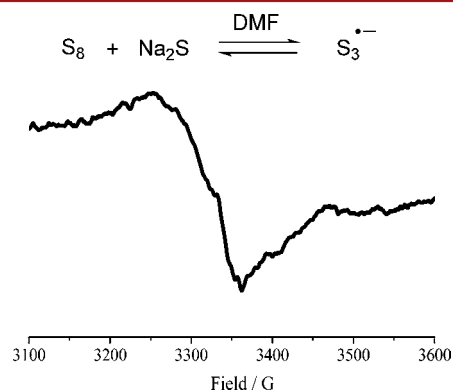
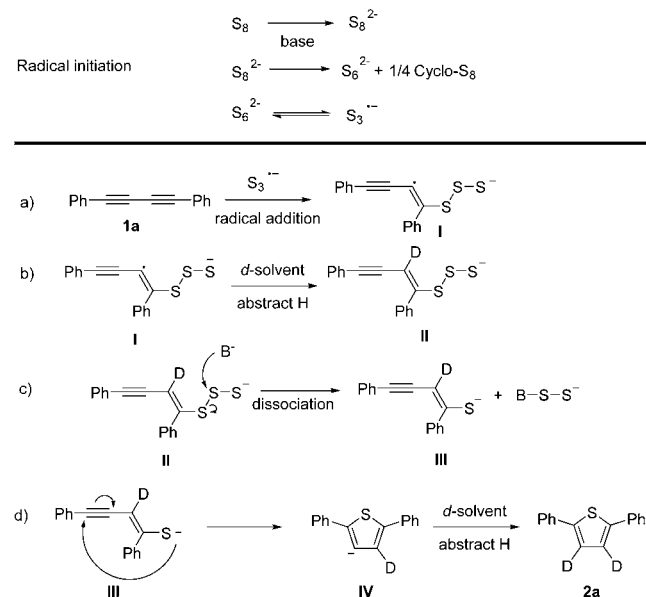


Figure 2. EPR studies of interaction between elemental sulfur and Na₂S.

there are some chemical equilibria between the trisulfur radical anion and sulfide ion (S²⁻) or polysulfides. It also means that even if the formation of a sulfide ion (S²⁻) occurred in the reaction, it would react with elemental sulfur to generate the trisulfur radical anion, which is the real reactive species.

A putative reaction pathway is listed in Scheme 3. First, elemental sulfur interacts with the base to generate the S₃^{•-}

Scheme 3. Proposed Mechanism



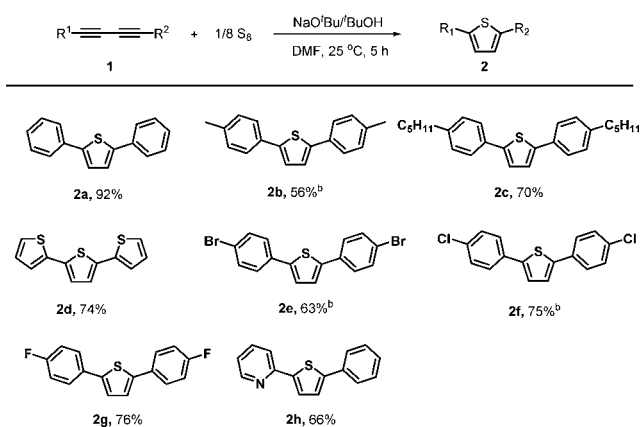
radical anion, which has been confirmed by our EPR results.^{4,9} Then the reaction proceeds through addition of the trisulfur radical to the alkyne **1a** to give the intermediate **I**. The initially formed vinyl radical **I** could abstract the hydrogen atom from solvent rapidly to give compound **II**. The dissociation of compound **II** would happen under strong basic conditions to

give a sulfur anion **III**, which would subsequently undergo intramolecular nucleophilic addition onto another triple bond to give anion **IV**. Then the anion **IV** could abstract a hydrogen atom from protic solvents, such as *t*BuOH, to form the product **2a**.

These results suggested that the trisulfur radical anion could play an essential role as an intermediate to generate corresponding thiophenes from 1,3-diynes. Thiophenes have multiple applications in medicinal, agricultural, and materials chemistry. Generally, they were prepared by the reaction of the corresponding 1,4-diketones with phosphorus pentasulfide¹¹ and hydrogen sulfide,¹² Lawesson's reagent,¹³ or Steliou's reagent.¹⁴ Recently, several synthetic approaches have been developed, such as metal-catalyzed tandem S-alkenylation of 1,4-diiodo-1,3-dienes with potassium sulfide and metal-free sulfur heterocyclization of 1,3-diynes with sodium hydrosulfide or sodium sulfide to form 2,5-substituted thiophenes.¹⁵ However, in these reports, it is unable to use elemental sulfur as the reagent to prepare the thiophenes. In this work, we realized a base-mediated intermolecular C–S bond formation reaction for the synthesis of thiophenes and their derivatives from 1,3-diynes and elemental sulfur under mild conditions.

Then, the generality of this radical addition reaction was investigated. As shown in Scheme 4, several electronically and

Scheme 4. Reaction Scope with 1, 3-Diynes in the Synthesis of 2, 5-Disubstituted Thiophenes^a



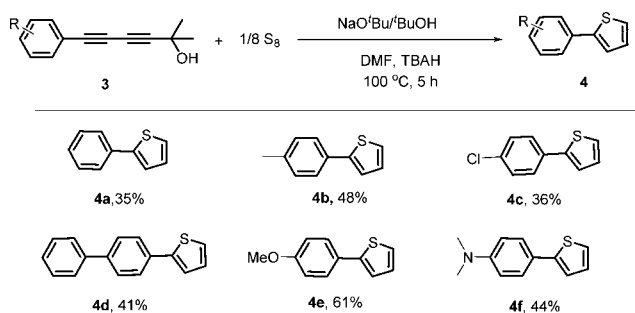
^aReactions were conducted at 25 °C for 5.0 h using **1** (0.30 mmol), sulfur powder (0.90 mmol), NaOtBu (1.8 mmol), and 1:3 (v/v) mixture of *t*BuOH/DMF (2.0 mL). Isolated yields are shown. ^bTemperature is 80 °C.

structurally diverse symmetrical and unsymmetrical aryl 1,3-diynes underwent the reaction smoothly with elemental sulfur, and various functional groups were well tolerated. Among them, the 1,3-diynes with either electron-donating groups (Scheme 4, **2b–2c**) or electron-withdrawing groups (Scheme 4, **2e–2g**) on the phenyl ring produced the corresponding 2,5-disubstituted thiophenes in good yields. It is noteworthy that a terthiophene (74%, Scheme 4, **2d**) was also successfully produced from 1,4-di(thiophen-2-yl) buta-1, 3-diyne in this system. Some examples of the synthesis of unsymmetrical 2,5-disubstituted thiophenes (Scheme 4, **2h**) were shown, and moderate yields were obtained. We found that the most important factor influencing the reaction yield is not the electronic effect of the substrates but their solubility in the solvent. For example, some substrates with poor solubility

(Scheme 4, **2b**, **2e**, and **2f**) need to increase the temperature to 80 °C to give good yields.

On the other hand, when we used tetrabutylammonium hydroxide (10% in Water) as the additive,¹⁶ and increased the temperature to 100 °C, 2-methyl-6-phenylhexa-3, 5-diyne-2-ol **3a** would react with elemental sulfur to form 2-phenylthiophene **4a** in one pot. As shown in Scheme 5, a series of

Scheme 5. Scope of Synthesis of 2-Substituted Thiophenes^a



^aReactions were conducted at 100 °C for 5.0 h using **3** (0.30 mmol), sulfur powder (0.60 mmol), NaOtBu (1.2 mmol), TBAH (10 mol %), and a mixture of 1:3 (v/v) *t*BuOH/DMF (2.0 mL). Isolated yields are shown.

derivatives of **3a** were tested. The reaction proceeded smoothly with this kind of 1,3-diynes bearing electron-deficient groups, as well as those containing electron-donating moieties, to give the corresponding products **4b–4f** in moderate yields (36–61%). It is a new approach for synthesizing the 2-substituted thiophenes, and a deeper understanding of this process is being pursued.

In conclusion, we have disclosed a base-promoted sulfur-centered radical generation mode via the interaction between elemental sulfur and NaOtBu. And through this radical generation mode, elemental sulfur, a cheap, environment-friendly, and commercially available reagent, was used for the direct synthesis of several substituted thiophenes. Reactions occurred through the interaction between a base and elemental sulfur to produce the key intermediate, the trisulfur radical anion.

■ ASSOCIATED CONTENT

§ Supporting Information

Experimental procedure, characterization data, and copies of ¹H, ¹³C, and ¹⁹F NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the 973 Program (2011CB808600, 2012CB725302), the National Natural Science Foundation of China (21390400, 21025206, 21272180, and 21302148), and

the Research Fund for the Doctoral Program of Higher Education of China (20120141130002) and the Program for Changjiang Scholars and Innovative Research Team in University (IRT1030). The Program of Introducing Talents of Discipline to Universities of China (111 Program) is also appreciated.

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