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Synthesis of Polysubstituted Thiophenes *via* Base-Induced [2+2+1] Cycloaddition Reaction of Alkynes and Elemental Sulfur

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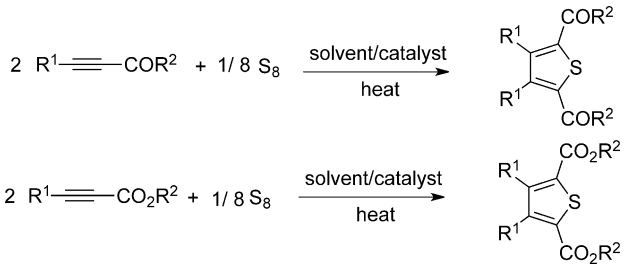
Abstract: A simple approach to polysubstituted thiophene derivatives is demonstrated. The synthesis is highlighted by the direct [2+2+1] cycloaddition reaction to construct carbon-sulfur and carbon-carbon bonds, without adding oxidizing, reducing and noble metal agents. All tested substrates provided their corresponding thiophene products in high isolated yields under the optimized conditions.

Keywords: alkynes; carbon-sulfur bond formation; [2+2+1]-cycloaddition; elemental sulfur; thiophenes

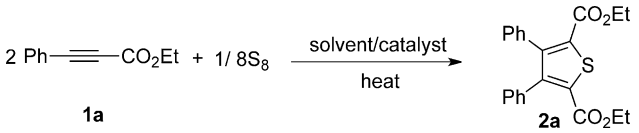
In recent years, the use of elemental sulfur in organic synthesis has received increasing attention for the construction of C–S bonds due to its low toxicity, ready availability, easy handling, lack of odour and yielding no metal waste. A number of unique synthetic applications of elemental sulfur have been reported.[1] The Nguyen group reported the synthesis of 2-hetarylbenzothiazoles in 2013[1d] and 2-aroylbenzothiazoles in 2015[1k] *via* redox reactions. Lei reported a facile base-promoted sulfur-centered radical generation mode and a single-step protocol for the synthesis of thiophene derivatives in 2014.[1j] Singh reported the synthesis of 2-substituted benzothiazoles *via* decarboxylative redox cyclization in 2015.[1m] Up to now, direct C–S bond formation by using elemental sulfur as the sulfur source has remained relatively undeveloped. This is mainly due to catalyst poisoning by elemental sulfur or the susceptibility of sulfur towards oxidative decomposition or oligomerization.[2]

As a case study, we disclose herein an elemental sulfur-mediated [2+2+1] cycloaddition reaction of alkynoates or ynones for the synthesis of polysubstituted thiophene derivatives (Scheme 1). Thiophene was first discovered by Victor Meyer in coal-tar light oil in 1882.[3] This heterocyclic moiety is one of the privileged scaffolds in chemistry[4] and is widely found in a variety of biologically active[5] and pharmaceutically useful compounds, such as plavix, spiriva, raloxifene, zileuton, and clopidogrel.[6] Furthermore, thiophene derivatives also find broad applications in the design and synthesis of novel organic functional materials due to their structural rigidity and specific electronic properties, such as organic semiconductors, organic solar cells, liquid crystals, field effect transistors, molecular wires etc.[7] In view of their applications in various fields, the development of new and efficient methods for the synthesis of polysubstituted thiophenes has received considerable attention and numerous synthetic routes have been reported in recent years.[8] The general synthetic methods for thiophene derivatives involve either direct functionalization of the preconstructed thiophene ring[9] or the construction of the thiophene ring *via* ring closure of appropriately substituted precursors.[10] The latter approach is apparently more versatile and thus represents an attractive but less well developed methodology. Among others, Paal–Knorr,[11] Fiesselmann,[12] Gewald[13] and



Scheme 1. Synthesis of thiophenes.

Table 1. Optimization of the reaction conditions.[a]



Entry	Solvent	Elemental Sulfur (S) (equiv.)	Time [h]	Base	Yield [%][b]
1	dioxane	S (1.0)	2	KOH	11
2	dioxane	S (1.0)	3	KOH	16
3	dioxane	S (1.0)	4	KOH	16
4	dioxane	S (2.0)	3	KOH	61
5	dioxane	S	3	KOH	82
6	dioxane	S(4.0)	3	KOH	82
7[c]	dioxane	S	3	KOH	27
8[d]	dioxane	S	3	KOH	82
9[e]	dioxane	S	3	KOH	24
10[f]	dioxane	S	3	KOH	trace
11	dioxane	S	3	CH_3ONa	78
12	dioxane	S	3	$NaHCO_3$	none
13	dioxane	S	3	Na_2CO_3	none
14	dioxane	S	3	AcONa	none
15	dioxane	S	3	DBU	trace
16	dioxane	S	3	DABCO	trace
17	dioxane	S	3	PPh_3	none
18	dioxane	S	3	DMAP	trace
19	DMSO	S	3	KOH	65
20	toluene	S	3	KOH	88
21[g]	DCE	S	3	KOH	46
22[g]	acetonitrile	S	3	KOH	31
23	DMF	S	3	KOH	68
24	toluene	S	3	NaOH	86

[a] Unless otherwise specified, all the reactions were carried out on **1a** at the 0.25 mmol scale with elemental sulfur 3.0 equivalents (based on S atom), base 1.0 equivalent, solvent 2.0 mL, reaction temperature 100 °C.
[b] GC yield.
[c] KOH 0.2 equivalent.
[d] KOH 1.5 equivalent.
[e] Reaction temperature: 60 °C.
[f] Reaction at room temperature.
[g] Reaction at reflux temperature.

Hinsberg reactions[14] are representative of the classical methods for thiophene synthesis.

At the outset of our experiments, we chose ethyl 3-phenylpropiolate (**1a**) and elemental sulfur as a reaction partners to optimize the reaction conditions including reaction time, the ratio of reactants, temperature, solvent and base (Table 1). From entries 1–3 in Table 1, it is seen that the reaction could be completed in 3 h and gave diethyl 3,4-diphenylthiophene-2,5-dicarboxylate **2a** in 16% GC yield. By varying the ratio of the reactants, we found that the optimal ratio of 3-phenylpropiolate (**1a**) to elemental sulfur (based on S atom) is 1:3. We then tried to optimize the yield of **2a** *via* changing the type and loading amount of base, reaction temperature and solvent. The experimental results showed that potassium hydroxide (KOH) and sodium methoxide (CH_3ONa) promoted the conversion to a high extent, but 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and other organic or inorganic bases performed poorly or even resulted in no desired product **2a**. An increase of the potassium hydroxide loading in the system from 1.0 to 1.5 equiv. (*vs.* **1a**) did not result in any noticeable increase in the yield of product, but there was a significant decrease of the yield when the KOH loading in system was decreased to 0.2 equiv. (entries 5, 7, and 8). It was also noticed that the reaction temperature dramatically affected the yield of the product. At 100 °C, an 82% yield of the product was obtained in 3 h with 3.0 equivalents of elemental sulfur and 1.0 equivalent of KOH (*vs.* **1a**). However, when the temperature was decreased to 60 C, only 24% yield was achieved. On a further decrease to room temperature, only a trace of product was obtained (entries 5, 9, and 10). Among the examined solvents (entries 19–23), toluene is more suitable than other solvents, leading to **2a** in 88 % yield (entry 23). Finally, this conversion was also tested by using NaOH as the base instead of KOH, the result indicated that NaOH was a good substitute for KOH, and gave almost the same result, producing the desired product **2a** with 86% GC yield (entry 24). Therefore, further experimental investigations were carried out with these optimized conditions [1.0 mmol substrate scale, elemental sulfur 3.0 mmol (based on S atom), KOH 1.0 equivalent, toluene 2.0 mL]. The structure of the product **2a** was confirmed by ^{1}H NMR, ^{13}C NMR and X-ray analysis (Figure 1).[15] For other new products, they mainly existed in the form of powders or oily liquids, therefore, their structures were confirmed by ^{1}H NMR, ^{13}C NMR and HR-MS analyses. Due to restricted rotation in some of the sterically congested molecules, their ^{13}C NMR spectra showed more than the expected number of signals.

With the optimized conditions in hand, the scope and versatility of the [2+2+1] cycloaddition reaction was then thoroughly examined, and the outcome is given in Table 2. The results indicated that all the tested alkynoates and ynones were ideal substrates. Notably, various functional groups, irrespective of their nature whether electron-donating or electron-withdrawing, were tolerated under the conditions. Besides, the location of the substituents on the aromatic rings was noticed to have an insignificant effect on the product yield. For example, fluoro-, chloro-, methyl-, ethyl-, methoxy- and other substituents on the aromatic rings as well as their locations as *ortho*- and *para*-substitution were all found to be compatible and all alkynoates or ynones **1** led to their corresponding products with excellent yields.

We all know that elemental sulfur could undergo a disproportionation reaction in the presence of base

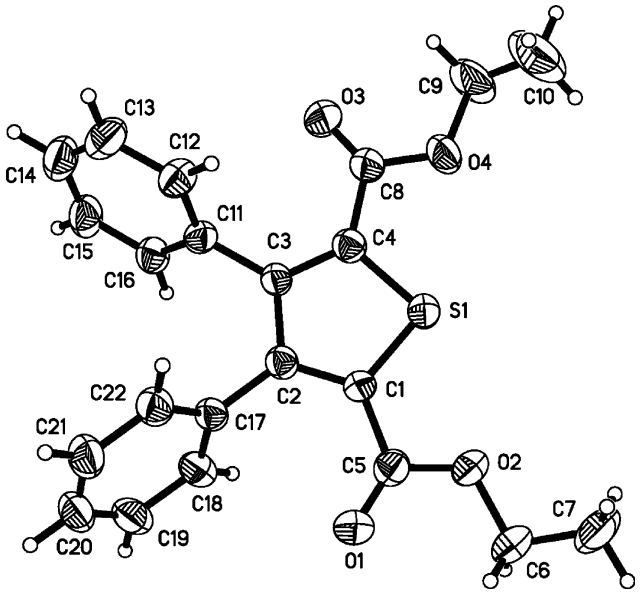
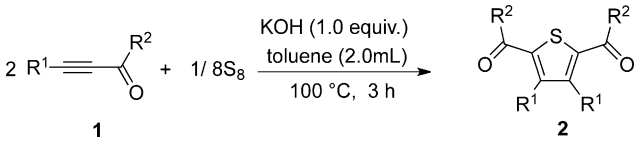


Figure 1. X-ray structure of diethyl 3,4-diphenylthiophene-2,5-dicarboxylate **2a**.

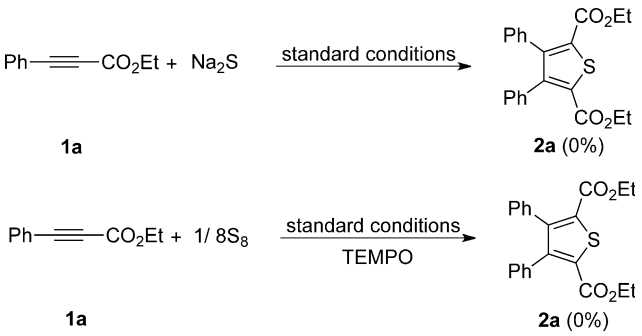
Table 2. Reaction of various alkynoates or ynones **1** with sulfur to form thiophenes **2a**.[a]



1 2

Entry	**1a–1s**	**2a–2s**	Yield [%][b]
1	$R^1 = C_6H_5/R^2 =$ OEt (**1a**)	**2a**	84
2	$R^1 = CO_2Et/R^2 =$ OEt (**1b**)	**2b**	85
3	$R^1 = CO_2Me/R^2 =$ OMe (**1c**)	**2c**	88
4	$R^1 = n$-pentyl/$R^2 =$ OMe (**1d**)	**2d**	76
5	$R^1 = R^2 = C_6H_5$ (**1e**)	**2e**	88
6	$R^1 =$ 4-ethyl$C_6H_4/R^2 = C_6H_5$ (**1f**)	**2f**	87
7	$R^1 =$ 4-(4-ethylcyclohexyl)$C_6H_4/R^2 = C_6H_5$ (**1g**)	**2g**	84
8	$R^1 =$ 4-(4-phenyl)C_6H_4 /$R^2 = C_6H_5$ (**1g**)	**2h**	86
9	$R^1 =$ 4-[4-(*n*-propyl)phenyl]$C_6H_4/R^2 = C_6H_5$ (**1i**)	**2i**	86
10	$R^1 = C_6H_5/R^2 =$ 4-MeC_6H_4 (**1j**)	**2j**	84
11	$R^1 = C_6H_5/R^2 =$ 4-ClC_6H_4 (**1k**)	**2k**	86
12	$R^1 = C_6H_5/R^2 =$ 2-ClC_6H_4 (**1l**)	**2l**	89
13	$R^1 = C_6H_5/R^2 =$ 4-MeOC_6H_4 (**1m**)	**2m**	83
14	$R^1 =$ 4-Me$C_6H_4/R^2 = C_6H_5$ (**1n**)	**2n**	88
15	$R^1 =$ 4-Me$C_6H_4/R^2 =$ 4-MeOC_6H_4 (**1o**)	**2o**	89
16	$R^1 =$ 4-Me$C_6H_4/R^2 =$ 4-ClC_6H_4 (**1p**)	**2p**	85
17	$R^1 =$ 4-Me$C_6H_4/R^2 =$ 4-FC_6H_4 (**1q**)	**2q**	84
18	$R^1 =$ 4-Me$C_6H_4/R^2 =$ 2-ClC_6H_4 (**1r**)	**2r**	83
19	$R^1 = R^2 =$ 4-MeC_6H_4 (**1s**)	**2s**	85

[a] Unless otherwise specified, all the reactions were carried out on **1** at the 1.0 mmol scale with elemental sulfur 3.0 equivalents (based on S atom), KOH 1.0 equivalent, toluene 2.0 mL.
[b] Isolated yield.



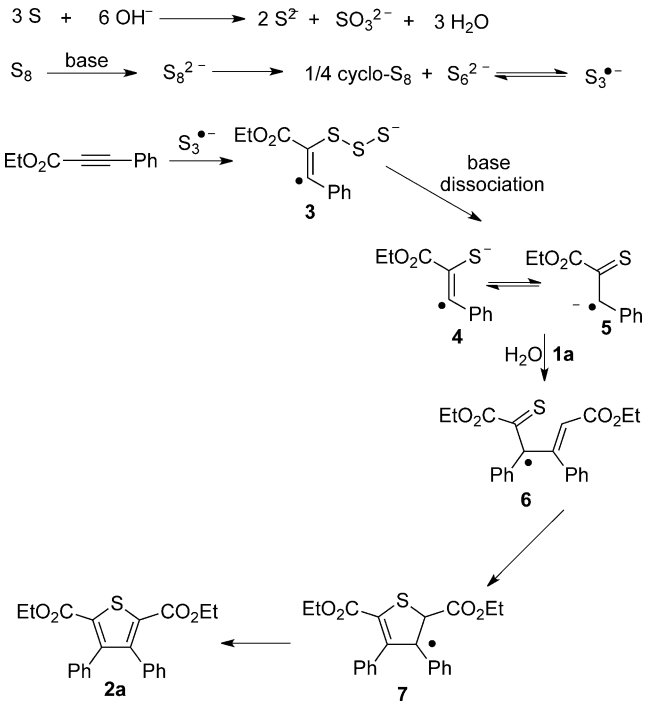
Scheme 2. Radical trapping and control experiments.

to produce a sulfide and a sulfite.[16] However, the sulfide ion was not found to be involved in the reaction based on the following experimental facts. During the process of the optimization of reaction conditions (Table 1), we examined several bases, but only potassium hydroxide (KOH) and sodium methoxide (CH_3ONa) could promoted the reaction, yielding the product **2a**, and other bases, such as sodium bicarbonate ($NaHCO_3$), sodium carbonate (Na_2CO_3) and sodium acetate (AcONa) failed to do so. If the sulfide ion had participated in the reaction, all investigated bases should have the capability to mediate the formation of target product **2a**.

In order to gain further insight into the nature of this transformation, two experiments were conducted (Scheme 2). Instead of elemental sulfur, sodium sulfide (Na_2S) was used to react with **1a** under the standard conditions but no desired product was obtained in this case, which further confirmed that the sulfide ion was not involved in the transformation. At the same time, the radical scavenger TEMPO completely inhibited the reaction and no product at all was obtained. These results indicated that the mechanism may involve a radical pathway.[1k]

On the basis of these observations as well as related reactions, we propose the mechanism shown in Scheme 3. The process could be initiated by the reaction of elemental sulfur with the base to generate the $S_3^{\bullet-}$ radical anion, which has been confirmed and reported by Lei and his co-workers.[1j] Subsequent addition of the trisulfur radical to the alkyne **1a** would generate the radical anion intermediate **3**. Under strong basic conditions, the S–S bond is fragile. Therefore compound **3** can easily dissociate to give **4** and **5**, which would subsequently undergo intermolecular nucleophilic addition onto another triple bond to give the labile radical **6**. The isomerization of **6** results in another radical **7**. Finally, the radical intermediate **7** goes through a hydrogen abstraction process[17] by the trisulfur radical under the reaction conditions to furnish the desired product.

In conclusion, we have developed a simple, atom economic and one-pot method to access polysubstitut-



Scheme 3. A mechanistic rationale for the synthesis of thiophenes.

ed thiophene derivatives. An appreciable range of alkynes can be used in this approach with elemental sulfur allowing the direct preparation of their corresponding thiophenes in high isolated yields. This method is highlighted by the direct [2+2+1] cycloaddition reaction for carbon-sulfur and carbon-carbon bond formation, without an added oxidizing, reducing or noble metal agent. More applications of this novel protocol and study of the detailed mechanism are currently underway.

Experimental Section

General Methods

All the reactions were carried out at 100 °C for 3 h in a round-bottom flask equipped with a magnetic stir bar. Solvents and reagents were purchased from Aldrich Chemicals or J & K Scientific Ltd, and were used as received. Petroleum ether (PE) refers to the fraction boiling in the 60–90 °C range. Thin-layer chromatography was performed using Qingdao-Haiyang 600 mesh silica gel plates (GF254), and samples were made visible with short-wavelength UV light (254 nm). Melting points were measured on a melting point apparatus equipped with a thermometer and are uncorrected. IR spectra were recorded on a Bruker Vector 22 spectrometer as KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded using solutions in $CDCl_3$ with tetramethylsilane as the internal standard. HR-MS were obtained on a Q-TOF micro spectrometer.

Typical Procedure: Diethyl 3,4-Diphenylthiophene-2,5-dicarboxylate (Table 2, entry 1)

A mixture of ethyl 3-phenylpropiolate (**1a**) (358 mg, 1.0 mmol), elemental sulfur (96 mg, 3.0 mmol), potassium hydroxide (KOH) (56 mg, 1.0 mmol) and toluene (2.0 mL) was added successively in a round-bottom flask, and the resulting solution was stirred for 3 h at 100 °C. The mixture was then subjected to purification by preparative thin-layer chromatography (PE-EtOAc, 20:1) to afford product **2a**.

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[15] CCDC 1426476 (compound **2a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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