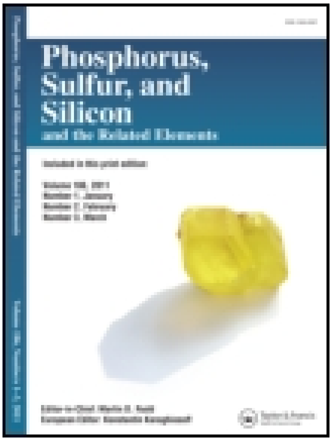

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Development of a Synthesis of Diphenylthiophenes via a One-Pot Reaction of Phenylacetylene and Sulfur

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Development of a Synthesis of Diphenylthiophenes via a One-Pot Reaction of Phenylacetylene and Sulfur

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The one-pot synthesis of a mixture of diphenylthiophenes **1** *and* **2** *from the reaction of phenylacetylene and sulfur under various reaction conditions was studied. Potential intermediates and a reaction pathway are postulated.*

Keywords Diphenylthiophenes; intermediates; phenylacetylene; reaction pathway; sulfur

INTRODUCTION

Thiophenes, one of the most fundamental heterocycles, occur abundantly as structural units in many natural and un-natural molecules. Thiophenes have potential applications in the flavor and pharmaceutical industries[1] and in conducting polymer applications.[2] They also are important intermediates in organic synthesis[3] and their synthetic study continues to attract much attention.

Thiophenes, generally, have been prepared by the reaction of the corresponding 1, 4-diketones with phosphorus pentasulfide and hydrogen sulfide,[4] Lawesson's reagent,[5] or Steliou's reagent.[6] Symmetric thiophenes can be prepared[7] from the condensation of β-chloroacroleins with benzyl bromides in the presence of sodium sulfide. Another route toward the synthesis of thiophenes is the one-pot reaction of phenylacetylene with sulfur, which so far has attracted little attention. This reaction has a rather bad reputation for not being useful for preparative purposes due to the formation of isomeric mixtures of thiophenes with poor yields. We present here the results of detailed investigations on

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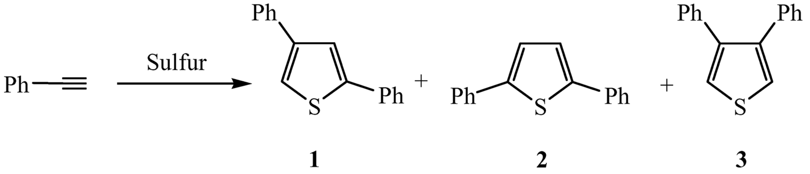
this subject. During this study, we were interested in investigating the possible intermediates of products to explain the contradictory results which have been reported thus far.[8] Finally, our current interest has led us to develop a practical one-step preparation of thiophenes (Scheme 1).



SCHEME 1

RESULTS AND DISCUSSION

Based on the literature procedure, heating a solvent-free mixture of phenylacetylene with sulfur gave 2, 4-diphenyl thiophene **1** in a 32% yield. We repeated this reaction at 100–120°C and obtained similar results (Table I, Entries a, b). We observed that the two reactants formed

TABLE I Formation of Thiophenes 1 and 2 From the Reaction of Phenylacetylene and Sulfur (1: 2)

					Yield (%)	
Entry	Method	Solvent	Temperature/°C	Time (min)	Total (**1** : **2**)[a]	Total (**5**: **4**)
a	SB[b]	—	100	60	45 (34: 11)	14 (5: 9)
b	SB	—	120	120	53 (33: 20)	17 (3: 14)
c	Reflux	Toluene[c]	120	240	2.5 (0.5: 2)	0.5 (0: 0.5)
d	Reflux	EG[d]	120	240	3 (1: 2)	1 (0: 1)
e	Reflux	EG	160	60	63 (13: 50)	24 (0: 24)
f	Reflux	EG	160	180	73 (10: 63)	11 (1: 10)
g	Reflux	EG	185	300	98 (18: 80)	—
h	Reflux	Decane	180	120	73 (46: 27)	14.5 (0: 14.5)
i	Reflux	DCB[e]	180	180	71 (38: 33)	16 (1: 15)
j	MW[f]	Toluene	—	5	18 (13: 5)	3 (0: 3)
k	MW	—	—	2	15 (4: 11)	4 (0: 4)
l	MW	—	—	2.3	62 (41: 21)	12.5 (1.5: 11)
m	MW	—	—	3.5	94 (55: 39)	1.5 (0: 1.5)
n	MW	—	—	5	94 (59: 35)	2.9 (0.5: 2.4)
o	MW	—	—	5	66 (34: 32)	14 (0: 14)
p	MW	EG	—	3	84 (54: 30)	8.5 (0: 8.5)

[a] In the product mixture, 2–4% of thiophene **3** was also Presented.
[b] SB = Sand bath.
[c] Phenylacetylene was recovered in 91%.
[d] EG = ethylene glycol.
[e] DCB = 1,4-dichlorobenzene.
[f] Under microwave heating (MW).

an opaque and homogenous phase at 95°C with a color changing to red. At this temperature, an exothermic reaction occurred, followed by loss of hydrogen sulfide. It is interesting to mention that conversion of sulfur to monoclinic sulfur occurred at 95°C and, therefore, it seems that there may be a relation between the temperature of the formation of the homogenous phase of the reactants and the temperature of the conversion of sulfur to monoclinic sulfur.

When we analyzed the crude reaction mixtures by GC-MS, we found 2, 5-diphenyl thiophene **2** and a trace amount of 3, 4-diphenyl thiophene **3** as new products of this reaction. This finding prompted us to investigate both the reaction pathway and the optimization of the reaction.

The identification of the products was generally performed by ^{1}H NMR and MS spectral analyses.

Solvent Effect

Table I shows selected experiments under various reaction conditions. Contrary to our expectations, refluxing a mixture of phenylacetylene and sulfur in toluene or heating it in ethylene glycol at 120°C for 4 h did not lead to the desired reaction and more than 95% of phenylacetylene was recovered (Table I, entries c, d). However, when the reaction mixture in ethylene glycol was heated at 160°C for 1 h, thiophenes **1** and **2** were formed followed by the loss of hydrogen sulfide (Table I, entries e and f). The best result was achieved by heating a mixture of phenylacetylene and sulfur at 185°C for 5 h, which led to formation **2** in an 80% yield (Table I, entry g). Surprisingly, the selective formation of product **2** is clear, which is in contrary to a solvent-free condition. Therefore, the best reaction conditions for obtaining the major amounts of **2** is described in the general procedures (see the Experimental Section) using ethylene glycol as a solvent. According to this procedure, products **1** and **2** were formed in a *ca.* 1:4 ratio.

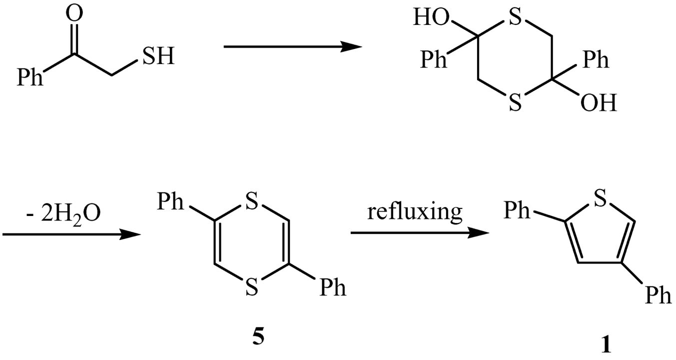
The reaction also was carried out in nonpolar, high boiling point solvents such as decane and 1, 4-dichlorobenzene (DCB). The experimental results showed a decrease in the total yield of thiophenes. Moreover, products **1** and **2** were formed in a *ca.* 2:1 ratio, showing a higher selectivity for **1** (Table I, entries h and i).

The solvent-free reaction of phenylacetylene with sulfur under microwave heating also was studied. During the irradiation, when the sulfur dissolved, an exothermic reaction took place, with the change of color from yellow to red. The exothermic reaction occurred after 2.3 min of irradiation. After this time, the yield of products suddenly increased as shown in Table I and Scheme 2. The best reaction conditions for obtaining the major amounts of **1** is described in the general procedures (see the Experimental Section) by 5 min irradiation under microwave condition (Table I, entry n). According to this procedure, products **1** and **2** were formed in a *ca.* 2:1 ratio.

The addition of ethylene glycol as a polar solvent to the reaction mixture resulted in the completion of the reaction in a shorter time (3 min) and gave **1** and **2** in a 54% and 26% yield, respectively (2:1 ratio). In this case, the color of the reaction mixture gradually changed, but without any explosion. The effects of the various solid supports under microwave irradiation also were studied, for which silica gel showed an improved efficiency in the yield of products.

Reaction Pathway

As shown in Table I, this reaction affords small amounts of 1, 4-dithiins **4** and **5** in addition to the thiophenes **1–3**, as indicated by GC-Mass spectrometric analysis.As outlined in Scheme 2, it is known in the literature[10] that 1, 4-dithiin **5** can be prepared in two steps from the self-condensation of α-mercaptoacetophenone under acid catalysis condition in a 50% yield. This method is restricted to the formation of isomer **5**. Furthermore, thionation of diketosulfides, followed by the cyclodehydration of the resulting monothiodiketone, led to selective preparation of dithiin **4**.[10]

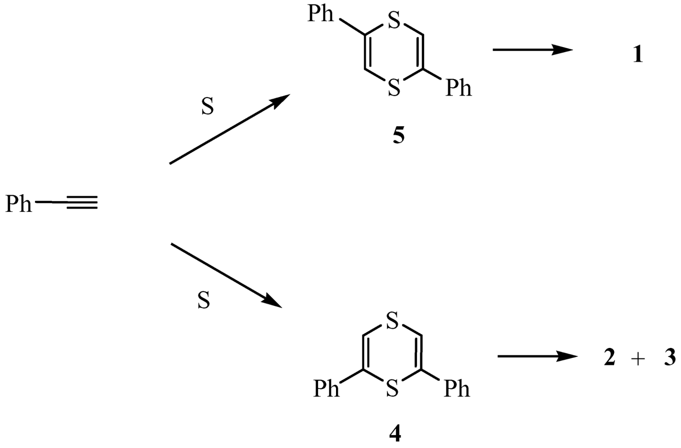


SCHEME 2

As reported in the literature,[11] 1, 4-dithiins **5** and **4** undergo the thermal extrusion of sulfur to afford the corresponding thiophenes **1** and **2**, respectively. Under thermolysis condition, 1, 4-dithiin **4** can easily be converted into the corresponding thiophene than that of 1, 4-dithiin **5**. Therefore, as shown in Table I, a higher amount of **5** is detected to confirm this result.

In accord with these facts, we propose the following sequence of steps of the formation of products **1** and **2**, as outlined in Scheme 3.

Further heating on the mixture of 1, 4-dithiins **5** and **4** leads to formation of products **1** and **2**. Therefore, predominant formation of thiophene **1** would result from this proposed path way:



SCHEME 3

CONCLUSION

In general, we have shown that phenylacetylene can be transformed into thiophenes through the simple heating with sulfur in a one-pot process in high yield. Surprisingly, unlike heating in a solvent-free condition, the reaction in decane or ethylene glycol needs higher temperatures to complete the reaction. We found that selective formations of products are strongly dependent on reaction media. In a polar medium, thiophene **2** selectively is formed, while, in nonpolar media, the major formation of **1** was observed.

In contrast to heating under solvent-free conditions, an improved yield was obtained by heating briefly with microwave irradiation.

We believe this one-pot reaction method provides a simple and highly efficienct process for the preparation of the substituted thiophenes.

EXPERIMENTAL SECTION

Caution: *Experiments should be carried out in an efficient hood to avoid exposure to noxious vapors of hydrogen sulfide.*

Products **1–5** were identified by GC-MS spectral comparison with authentic specimens. Column chromatography was performed on Merck silica gel (0.040–0.063 particle size). For GC-MS analysis, a Fision instruments gas chromatograph 8000 equipped to a mass detector (Trio 1000) with 70 ev was used. A 60 m x 0.25 mm column packed with WCOT fused silica gel CP-sil 5 CB was employed. The carrier gas was helium and the inlet pressure was 14 psi.

Reaction of Phenylacetylene and Sulfur

(a) Under Refluxing Condition

A mixture of phenylacetylene (1.0 mmol) and sulfur (2.2 mmol) in ethylene glycol (30 mL) was heated in an oil bath at 185 °C for 5 h. The dark red reaction mixtures were directly analyzed by GC-MS and/or were subjected to column chromatography. The products **1** and **2** were formed in a 98% yield (in a *ca.* 1:4 ratio). Careful chromatography on the silica gel and by gradual elution with light petroleum ether-benzene afforded products **1** and **2** in a 15% and 73% yield, respectively. Further crystallization from ethanol gave pure products. The identification of the isolated products generally was performed by ^{1}H NMR and MS spectral analyses.

(b) Under Pyrolysis Condition

A mixture of phenylacetylene (1 mmol) and sulfur (2.2 mmol) in an open pyrex glass flask was heated in sand/oil bath for 120 minutes. Based on a GC-MS analysis, 33% of **1** and 20% of **2** was obtained. After 2 h, the reaction was not completed and 20% of phenylacetylene also was recovered.

(c) Under Microwave Condition

A mixture of phenylacetylene (1 mmol) and sulfur (2.2 mmol) in an open Pyrex glass flask was exposed to microwave irradiation at 900 W for 5 min with 30 s intervals.[12]

After 2.3 min irradiation, an explosive reaction was observed and the color of the mixture changed from yellow to red. The crude products were directly analyzed by GC-MS and afforded the total products **1** and **2** in a 94% yield in a *ca.* 2:1 ratio. A careful chromatography on silica gel and by gradual elution with light petroleum ether-benzene afforded products **1** and **2** in a 55% and 27% yield, respectively. Further crystallization from ethanol gave pure products.

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[12] The microwave oven used for this study was a domestic National model NN-6755 with 7 power setting (90-900 W).